In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 16-701V

Filed: March 23, 2022

LISA ANTALOSKY, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent	TO BE PUBLISHED Ruling on Entitlement; Influenza (Flu) Vaccine; Bronchiolitis Obliterans

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Traci R. Patton, U.S. Department of Justice, Washington, DC, for Respondent

RULING ON ENTITLEMENT[1]

Oler, Special Master:

On June 16, 2016, Lisa Antalosky ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*[2] (the "Vaccine Act" or "Program"). Petitioner alleges that she suffered from advanced obstructive lung disease secondary to constrictive bronchiolitis following receipt of her October 15, 2014 influenza ("flu") vaccine. Pet. at 1. For the reasons discussed in this ruling, I find that Petitioner is entitled to compensation.

[1] This Ruling will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Ruling will be available to anyone with access to the internet**. As provided in 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Ruling's inclusion of certain kinds of confidential information. To do so, each party may, within 14 days, request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, this Ruling will be available to the public in its present form. *Id.*

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

I. Procedural History

On June 16, 2016, Lisa Antalosky filed a petition seeking compensation under the Vaccine Act, alleging that she suffered from advanced obstructive lung disease secondary to constrictive bronchiolitis following receipt of her October 15, 2014 flu vaccination. Pet. at 1.

Petitioner filed medical records on August 1, 2016. Exs. 1-15. Petitioner filed additional medical records on August 9, 2016. Exs. 16-18. She then filed a statement of completion on August 9, 2016. ECF No. 11.

On September 9, 2016, Respondent filed a status report requesting that Petitioner file additional medical records. Petitioner filed records on November 11, 2016, and an amended statement of completion on the same date. Ex. 19.

On January 26, 2017, Respondent filed his Rule 4(c) Report, asserting that the case was not appropriate for compensation and should be dismissed. Resp't's Rep.

Petitioner filed her first expert report from Dr. Eric Gershwin on May 9, 2017. Ex. 20. Petitioner filed supporting medical literature on the same date. Exs. 21-30.[3] Petitioner filed Dr. Gershwin's curriculum vitae on February 13, 2020. Ex. 69.

On August 17, 2017, Respondent filed rebuttal expert reports from Dr. Derek Byers and Dr. Emil Bardana. Exs. A, C. Supporting medical literature for Dr. Byers' report was filed as Exs. A1-A8.[4] Supporting medical literature for Dr. Bardana's report was filed as Ex. C1-C9.

Petitioner filed a second expert report from Dr. Gershwin on April 2, 2018, addressing the points raised by Dr. Bardana and Dr. Byers in their reports. Ex. 32.

On June 28, 2018, Respondent filed rebuttal reports from Dr. Byers and Dr. Bardana. Exs. E, F. Petitioner filed additional medical records on January 13, 2020. Exs. 44-49; ECF No. 53.

The parties filed joint pre-hearing submissions on January 22, 2020. Petitioner filed highlighted versions of her previously filed medical literature on January 23, 2020. Exs. 50-68.

Petitioner filed her pre-hearing brief on January 23, 2020. ECF No. 65. Respondent filed his pre-hearing brief on the same date. ECF No. 66. The parties filed additional joint prehearing submissions on February 6, 2020. ECF No. 69.

I held an entitlement hearing in this case on February 20, 2020. Minute Entry dated 2/20/2020. Petitioner filed a post-hearing brief on May 8, 2020. ECF No. 75. Respondent filed a

[3] Petitioner re-filed certain medical literature on January 22, 2020. Exs. 14, 24, 25, 28, and 29.

[4] Respondent re-filed this medical literature as highlighted versions on February 6, 2020. Exs. A1-A7.

post-hearing brief on July 7, 2020. ECF No. 76. Petitioner filed her reply brief on August 5, 2020. ECF No. 77.

This matter is now ripe for adjudication.

II. Medical Records

A. Relevant Pre-Vaccination History

Lisa Antalosky was born in 1973. Ex. 3 at 4. She was 41 years-old in October of 2014. *Id*.

Prior to October of 2014, Petitioner was generally in good health with a medical history of hypothyroidism, seasonal allergies, anxiety/depression, and irritable bowel syndrome. Ex. 3 at 4. With respect to respiratory issues, she had bronchitis in middle school and her medical records indicate that she had pneumonia at age 12.[5] Ex. 4 at 1.

On January 10, 2012, Petitioner presented to Geisinger Medical Center with complaints of ear pain, sore throat, nasal congestion, cough, and headache. Ex. 19 at 16-19. Her examination was unremarkable except for an inspiratory wheeze without rhonchi or localizing rales. *Id*. She was diagnosed with an acute upper respiratory infection with acute bronchospasm and she was prescribed an Albuterol sulfate inhaler for wheezing, two puffs every four to six hours as needed. *Id*. The medical records indicate that she continued to use the Albuterol inhaler through at least May 14, 2012. Ex. 19 at 39.

An immunization summary prepared by Geisinger Medical Center shows that Petitioner had four prior seasonal influenza vaccinations in 2007, 2008, 2011, 2012. Ex. 3 at 1.

B. Post-Vaccination History

Petitioner received the flu vaccine on October 15, 2014. Ex. 9 at 1.

On November 29, 2014, Petitioner saw her primary care physician (PCP), Dr. Hood, at Geisinger Medical Center with complaints of a cough, wheezing, and shortness of breath. Ex. 3 at 8; Ex. 8 at 2. Dr. Hood prescribed prednisone and albuterol. *Id*.

Two days later, on December 1, 2014, Petitioner presented to the Emergency Department at Gsach-Geisinger Shamokin Area Community Hospital with a chief complaint of shortness of breath. Ex. 8 at 2. She reported having an upper respiratory infection ("URI") "that started several weeks ago." *Id*. Petitioner reported that subsequent to the URI, she developed a cough and shortness of breath that was progressively getting worse. *Id.* The medical records note that she had been evaluated by Dr. Hood two days prior and was started on oral steroids and an albuterol inhaler. *Id*. On examination, Ms. Antalosky was found to be hypoxic on room air with diminished

[5] Although Petitioner's medical records indicate that she developed pneumonia as a child, she discussed this during the entitlement hearing. Petitioner testified that although she told Dr. Simonelli that she had pneumonia, she is not sure whether she actually had pneumonia or bronchitis. Tr. at 12-13.

lung sounds and diffuse expiratory wheezing. *Id.* at 4. A chest x-ray and echocardiogram were unremarkable. *Id*. She was treated with duo-nebulizers and two albuterol nebulizers with no improvement. *Id.*

Petitioner was admitted to the hospital for further examination. Ex. 8 at 6-9. Ms. Antalosky was examined by a general internist who noted that she had been experiencing a persistent dry cough, shortness of breath and wheezing for the past three to four weeks, and complained of a runny congested nose and sore throat but no fever or chills. *Id.* at 6. With respect to the onset of her signs and symptoms, the medical record notes the following: "[p]atient describes her symptoms started few weeks back and [became] progressively worse with cough and shortness of breath…" *Id.* at 6. The doctor suspected that Petitioner was suffering from a viral illness; the impression listed in the medical record was "acute hypoxic respiratory failure secondary to upper respiratory viral illness." *Id.* at 8. However, testing for Influenza A and B, Respiratory Syncytial virus, Parainfluenza viruses 1, 2, 3, and 4, Human Metapneumovirus, Rhinovirus, Adenovirus, Coronaviruses HKU1, NL63, 229E, and OC43, Bordetella, Pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae were all negative. *Id.* at 13, 17.

Petitioner was discharged from the hospital on December 5, 2014 in stable condition after being treated with steroids and bronchodilators. Ex. 8 at 10-12. She had no discharge diagnosis, but resolved hospital problems were listed as acute bronchospasm, viral illness, hypoxia, and wheezing. *Id.* at 10. She was instructed to complete her course of oral steroids and was started on Advair, duo-nebulizers, and Albuterol. *Id.* at 11-12.

On December 9, 2014, Petitioner saw a physician assistant (PA) Stephanie Christian for a follow up regarding her recent hospitalization. Ex. 3 at 8. Petitioner reported feeling a little better but she was still coughing and continued to feel winded. *Id*. Upon examination, she was found to have minimal nasal congestion and scattered expiratory wheezes but no dullness to percussion. *Id*. She was assessed with reactive airway disease (asthma) and a viral illness, and she was instructed to continue taking her current medications. *Id*. at 9.

Petitioner visited Dr. Hood on December 16, 2014, complaining of coughing and wheezing, chest pains, and worsened shortness of breath. Ex. 3 at 18. Petitioner reported that she was short of breath when walking and talking, and her nose was stuffy but not runny. *Id.* D-Dimer testing ruled out deep venous thrombosis, and an EKG was unremarkable *Id.* at 26-27. Dr. Hood assessed her with shortness of breath and chest pain with probable viral infection. *Id.* at 27.

On December 17, 2014, Petitioner had an initial consultation with nurse practitioner (NP) Kandace Gonzalez at the Geisinger Thoracic Department pursuant to Dr. Hood's referral. Ex. 4 at 1. Petitioner reported experiencing shortness of breath for the last several weeks. She further indicated that "She received a flu vaccine in October at CVS and noticed a slight wheeze since getting the injection." *Id.* The record further indicates that "She started with head cold symptoms 1-2 weeks prior to Thanksgiving and shortness of breath progressively got worse." *Id*. Petitioner reported that she had been running three to four miles every other day until October, when she stopped due to her schedule. *Id.* It was noted that she had moved into her brother's home and that her former home "had visible mold in the basement." *Id.* at 2. A physical examination revealed shallow breathing and a dry cough with decreased breath sounds. *Id*. The assessment was shortness

of breath, cough, hypoxemia, possible asthma, and possible bronchiolitis. *Id.* at 4. NP Gonzalez recommended that Petitioner continue taking her prescribed medications. *Id.* at 5.

Petitioner met with pulmonologist Dr. Simonelli on December 17, 2014. Ex. 4 at 5. Dr. Simonelli noted that Petitioner was well until October of this past year, when she "developed worsening wheezing, chest tightness and dyspnea following a flu vaccination". *Id.* When seen on December 17, Dr Simonelli noted Petitioner developed "desaturation from 93% to 87% with a short walk, her breathing was labored, and she developed tachycardia to 126 BPM from her baseline @ 72 BPM after walking only about 100 feet." *Id.* Petitioner's exam was notable for distant breath sounds. *Id.* Dr. Simonelli indicated that Petitioner's spirometry revealed very severe airflow obstruction and probable air trapping supportive of severe airway disease. *Id.* at 5, 29. He opined that asthma was unlikely but that bronchiolitis was possible, and he recommended that Petitioner continue on 30mg prednisone daily, increase her dosage of Advair, add tiotropium, and continue her nebulizer treatments. *Id.* at 5-6.

Petitioner returned to see NP Gonzalez and Dr. Simonelli on December 22, 2014, and reported that her breathing was worse even while at rest. Ex. 4 at 35. An examination revealed that Petitioner's respiratory rate was in the 60's after mild exertion and decreased to 36 after five minutes of rest, and her heart rate increased from 105 to 130bpm. *Id.* at 35-36. Dr. Simonelli recommended that she be admitted to Geisinger Medical Center for further management and testing. *Id.* at 36. The problems list on admission included possible bronchiolitis, hypoxemia, dyspnea, and possible asthma. *Id.* at 61. Petitioner was discharged on December 24, 2014 on 60mg/day of prednisone and advised to return to the outpatient pulmonary clinic in one week. *Id.* at 61.

On December 31, 2014, Petitioner followed up at the pulmonary medicine clinic with NP Gonzalez and Dr. Simonelli. Ex. 4 at 61. She reported no improvement in her condition since being treated with the higher dose of prednisone. *Id.* Her oxygen desaturation had worsened to 80% on walking fewer than 15 feet and her spirometry had worsened as well. *Id.* at 63. She had an SaO_2 of 92%, mild conversational dyspnea, and diminished breath sounds bilaterally. *Id.* at 62. The pulmonary function report from December 23, 2014 confirmed that Petitioner's condition was obstructive, and her lab work revealed a positive ANA titer of 1:160 in a speckled pattern. *Id.* at 62-63. Dr. Simonelli's assessment remained bronchiolitis of uncertain cause, and he recommended a possible lung biopsy if her condition did not improve. *Id.* at 63.

Petitioner returned to the pulmonary clinic on January 12, 2015, and reported that her breathing was unchanged, although she thought she was coughing less. Ex. 4 at 93. She continued to have chest/rib discomfort that was exacerbated by coughing and sneezing. *Id.* She was using supplemental oxygen with exertion to help her get things done around the house. *Id.* Her Prednisone dose was decreased from 60mg to 40mg, and the assessment continued to be possible bronchiolitis, dyspnea, and exertional hypoxia. *Id.* at 94.

On January 26, 2015, Petitioner was evaluated for interstitial lung disease by Dr. Facktor, director of the Geisinger Thoracic Surgery Clinic, pursuant to Dr. Simonelli's referral. Ex. 5 at 23. Dr. Facktor noted that Petitioner had been experiencing progressive exertional dyspnea for the past three months, and that any significant exertion caused her shortness of breath. *Id.* Dr. Facktor

reviewed Petitioner's CT of the chest from December 22, 2014, and assessed her with progressive symptomatic interstitial lung disease. *Id.* at 26. Dr. Facktor recommended a diagnostic lung biopsy. *Id.*

Petitioner returned to the pulmonary clinic on January 29, 2015 for a follow up of her dyspnea and hypoxemia. Ex. 5 at 58. The record notes that Petitioner will have a lung biopsy on February 2, 2015. *Id.*

On February 4, 2015, Petitioner was admitted to Geisinger Medical Center and underwent three diagnostic infiltrate lung wedge biopsies. Ex. 7 at 18, 22. She was discharged on February 7, 2015 with a principal diagnosis of bronchiolitis. *Id.* at 21. Because she had a small intermittent forced expiratory air leak, she was discharged with a chest tube that was later removed on February 10, 2014. *Id.* at 23; Ex. 5 at 90.

On February 11, 2015, the biopsy report for Petitioner's three lung specimens revealed evidence of small airway disease showing acute and chronic bronchiolitis with peribronchiolar aggregates of foamy histiocytes, rare poorly formed granuloma, peribronchiolar metaplasia, as well as patchy mild interstitial fibrosis. Ex. 7 at 27-29.

On February 18, 2015, Petitioner had a follow up appointment at the pulmonary medicine clinic. Ex. 5 at 100. She reported that her cough had increased, that her exercise tolerance was getting worse, and that she had difficulty breathing at night. *Id*. Dr. Simonelli explained to Petitioner that her diagnosis post-biopsy was constrictive bronchiolitis. Ex. 6 at 2. He noted that there was no evidence of an underlying inflammatory disease that could have caused her condition. *Id.* Dr. Simonelli indicted that "the cause of her bronchiolitis is not known, though the temporal relationship to her receiving a flu vaccine is provocative." *Id*. Petitioner expressed her interest in pursuing a lung transplant. *Id*.

On March 26, 2015, Petitioner had an initial consultation at the University of Pennsylvania Perelman Hospital with Dr. Ahya. Ex. 6 at 46-48. The medical records note that "Lisa reports that she was in her usual state of health until October 2014. At that time, she developed respiratory viral infection symptoms-cough wheezing and dyspnea. After a week or so, these symptoms did not improve. In fact, by mid-November, she had significant exertional dyspnea." *Id.* at 46. Dr. Ahya assessed her with advanced obstructive lung disease secondary to constrictive bronchiolitis likely related to recent respiratory viral infection, and agreed that she should be evaluated to determine her candidacy for lung transplantation. *Id*. at 13, 21.

On April 12, 2015, Petitioner was admitted to the ER of GWV - Geisinger Wyoming Valley Hospital in acute respiratory distress. Ex. 2 at 2. This record notes that "onset of initial difficulty breathing occurred after receiving flu vaccination on 10/15/2014." *Id.* Her initial examination revealed decreased breath sounds bilaterally with wheezes in both bibasilar lung fields. *Id.* at 6. A chest X-ray revealed a small focal opacity in the right upper lobe that could represent infiltrate or post-surgical changes. *Id.* at 9. The University of Pennsylvania Transplant Team was contacted, and they agreed to take Petitioner once her condition stabilized. *Id.* at 3. She was intubated, placed on a ventilator, and transferred to ICU where she was monitored until her condition became stable.

Id. at 9. She was discharged five days later with a diagnosis of acute respiratory distress secondary to constrictive bronchiolitis. *Id*.

Petitioner followed up with the pulmonary medicine clinic on April 30, 2015. Ex. 6 at 84. She reported having to cancel her transplant evaluation because her transportation fell through. *Id*. Petitioner was noted to be ill-appearing and in mild respiratory distress, and she was encouraged to reschedule the transplant evaluation. *Id*. at 85-86.

Petitioner also followed up with her primary care physician on April 30, 2015. Ex. 3 at 33. She reported doing better until she began to taper off her prednisone, but her breathing improved a bit once she increased the dose. *Id.* at 36. Her assessment continued to be constrictive bronchiolitis with exertional dyspnea and recent hospitalization for pneumonia. *Id*. Petitioner reported that she would follow up with her transplant consultation once she was stable. *Id*.

On May 18, 2015, Petitioner saw a physician assistant at Geisinger Medical Center reporting that she would be admitted to the University of Pennsylvania to undergo her transplant evaluation. Ex. 3 at 45-48, 36. She was noted to have a depressive disorder due to her ongoing health problems and bronchiolitis with exertional dyspnea. *Id.* at 48.

Petitioner was admitted to the University of Pennsylvania Hospital on May 19, 2015, due to increased need for oxygen and increased dyspnea. Ex. 6 at 23. A chest X-ray and CT scan revealed that she had pneumonia as well as a lesion on her liver but no evidence of cardiac disease *Id*. Petitioner was treated empirically with intravenous antibiotics, steroids, and Bactrim while in the hospital. *Id.* She also underwent left and right cardiac catheterization as part of her lung transplant evaluation. *Id*. at 24. She was discharged on May 27, 2015. *Id*. Petitioner's discharge summary indicates that Petitioner has biopsy proven bronchiolitis obliterans that is "suspected to have an underlying autoimmune etiology (response to flu immunization, +ANA)." *Id.*

On June 9, 2015, Dr. Ahya indicated that Petitioner had "chronic end-stage lung disease failing maximal medical therapy." Ex. 7 at 1. She was not currently eligible to be placed on the lung transplant list because of several unresolved issues including the need for an ultrasound exam of her liver and the need to demonstrate that she can meet health management expectations. *Id.* The lung transplant committee determined that Petitioner was a likely candidate for lung transplant in the near future, pending resolution of the identified issues. *Id.* at 6.

Petitioner underwent a bronchoscopy[6] on October 7, 2015, that revealed "necrotizing granulomatous inflammation with acid fast bacilli compatible with mycobacterial infection." Ex. 10 at 2, 7.

On September 8, 2015, Petitioner visited Dr. Ahya for a follow-up. Ex. 15 at 1-6; 8-13. She reported that since her last visit she had two exacerbations of her disease triggered by upper

[6] Bronchoscopy is an "examination of the bronchi through a bronchoscope." *Bronchoscopy*, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=7077 (last visited on March 8, 2022).

respiratory tract infections, but her symptoms returned to their recent baseline after treatment with antibiotics and corticosteroids. *Id.* at 1. She reported a mild increase in exertional dyspnea, and she continued to have wheezing but no chest pain, palpitations, lightheadedness, or dizziness. *Id.* A physical examination revealed markedly diminished breath sounds bilaterally with no wheezes. *Id.* at 2. Petitioner was assessed with advanced obstructive lung disease secondary to constrictive bronchiolitis likely related to recent respiratory viral infection. *Id.* at 6. Dr. Ahya advised her to schedule a surgical consent appointment for lung transplantation. *Id.*

On October 13, 2015, Petitioner presented to the emergency department of Geisinger Medical Center complaining of shortness of breath and coughing that had worsened over the past two weeks. Ex. 10 at 7. A chest x-ray showed an increasing bilateral lower lung air space disease with suspicions for worsening infection, and she was admitted to the internal medicine department with diagnoses of bronchiolitis and chronic respiratory failure with hypoxia. *Id*. at 4. Petitioner was discharged four days later, on October 17, 2015, with the following diagnoses: respiratory failure, acute-on-chronic; SIRS (systemic inflammatory response syndrome); obliterative bronchiolitis; mycobacterium avium-intracellulare infection (MAC), irritable bowel syndrome and hypothyroidism. *Id*. at 13. She was started on daily MAC antibiotic therapy. Ex. 16 at 299.

On October 28, 2015, Petitioner was seen at the Geisinger Medical Center ER for evaluation of acute respiratory distress. Ex. 17 at 451-54. After evaluation and initial treatment in the ER she was admitted to the Surgical ICU. *Id.* at 456. The initial impression was bronchiolitis and *Mycobacterium avium* complex infection with acute and chronic hypoxic respiratory failure. *Id.* at 471. A respiratory examination revealed some bibasilar crackles and faint expiratory wheezing, and she was to continue treatment for her *Mycobacterium avium* complex. *Id.* at 474. A palliative medicine consult discussed the need for advanced illness planning, and she appointed her boyfriend as a medical decision maker. *Id.* at 384. She was discharged on November 2, 2015.

From October of 2015 through April of 2016, Petitioner continued to follow up at Geisinger Medical Center. Her assessment remained Mycobacterium avium complex infection with severe constrictive bronchiolitis. She continued antibiotic therapy for her Mycobacterium avium complex, and she was prescribed oral morphine to help with her shortness of breath/air hunger. Ex. 17 at 427-30, 471-74; Ex. 18 at 506-09, 680-83, 856-58.

On April 11, 2016, Petitioner returned to the University of Pennsylvania's Lung Transplant Office. Ex. 15 at 8-13. She reported clinical improvement with treatment for her mycobacterial infection. Ex. 15 at 13. She continued to have some wheezing and exertional dyspnea but no chest pain, lightheadedness or dizziness. *Id.* at 8. She was scheduled to undergo a chest CT scan and an echocardiogram, and the staff was going to make sure her medical insurance would cover lung transplantation. *Id*. at 13. She was advised to schedule a follow-up exam in two to three months. *Id*.

In 2016, Petitioner was placed on the waiting list for a lung transplant, and was called twice for a possible transplant, but both fell through. Ex. 45 at 67.

In 2017, Petitioner was taken off the transplant list because her boyfriend passed away, and she no longer had a means of transportation to Philadelphia. Ex. 44 at 5.

On November 30, 2018, Petitioner's pulmonologist, Dr. Mehta, described her condition as very severe but stable. Ex. 48 at 211. At that time, she had not been reinstated on the active transplant list. *Id.* at 210.

On January 24, 2019, Petitioner presented to Family Practice Center for an annual gynecological exam and a check-up. Ex. 44 at 36. During this visit, Petitioner related that "she had a flu vaccination in 2014 which led to pulmonary mycobacterium avium infection which has caused permanent damage to her lungs." *Id.* The record notes that Petitioner uses oxygen daily, both during exertion and when she is sleeping. She stated that "without the oxygen, she would not be able to walk around without experiencing shortness of breath." *Id.*

In a record dated April 19, 2019, the influenza vaccine is listed as an allergy that caused lung damage. Ex. 45 at 4; Ex. 48 at 270.

No additional medical records relevant to my determination of the issues presented in this case have been filed.

III. Petitioners' Affidavits and Testimony

A. Petitioner's Affidavits

Petitioner states that she was in good health prior to her vaccination in October of 2014. Ex. 11 at 1. The day after her vaccination, she "started to notice a slight wheeze that [she] never had before." *Id*. About four days later, she "started to have a dry cough and [she] noticed [she] was getting out of breath when [she] was doing normal activities like having a conversation or walking around [her] house." *Id*.

When her wheezing did not resolve within a few weeks, she went to see her primary care physician at the end of November 2014. Ex. 11 at 1. She was prescribed prednisone and an inhaler, but she was not diagnosed with an upper respiratory infection. *Id*. She was hospitalized two days later with a discharge diagnosis of bronchospasm and viral illness although the doctors did not find any viral infection. *Id*. at 2.

Dr. Simonelli diagnosed her with bronchiolitis following her lung biopsy, and he told Ms. Antalosky that the most likely cause for her lung disease was a reaction to the flu shot she received in October of 2014. Ex. 11 at 2. He also told her that her only option was a double lung transplant. *Id*.

As of the date of filing of this affidavit, Ms. Antalosky was working with the University of Pennsylvania lung transplant department to get on the lung transplant list. Ex. 11 at 2. She stated that her entire life has changed because of her illness. *Id*. She used to be very active, but she can no longer exert herself. *Id*. She gets winded just trying to have a conversation, and she now needs to be on oxygen constantly. *Id*.

B. Testimony

Petitioner testified at the entitlement hearing. Hearing Tr. at 4.

Petitioner testified that in early 2012, she was diagnosed with an upper respiratory infection ("URI") which eventually led to bronchitis. Tr. at 11. Petitioner testified that following use of an inhaler and medication, the infection "went away" *Id.* She also testified that she could only recall one instance in her childhood that she had an URI, and wasn't sure if it was eventually classified as bronchitis or pneumonia. *Id.* at 12-13.

Petitioner testified that in April 2013, she was seen for an edema, where her "ankles were swollen, and especially [her] eyelids and underneath [her] eyes." *Id.* at 14. She testified she was given a diuretic, which "seemed to help", but the problem simply resolved by itself "in late 2013 or so" *Id.* at 14.

She testified that prior to October 2014, she suffered from hypothyroidism, irritable bowel syndrome ("IBS") and seasonal allergies. Tr. at 6-10. She testified that her conditions were well managed with medication, although stress typically worsens her IBS. *Id.* at 9. She also testified that her seasonal allergies generally did not cause any lung symptoms. *Id.* at 17.

Petitioner testified she received on flu vaccine on October 15, 2014, at Rite Aid pharmacy. Tr. at 14. Petitioner stated that she had received the flu vaccine before and had never had a prior reaction to it. *Id.* She testified that the day after the vaccine she was "doing a house run to…make sure everybody was…doing what they were supposed to do. And I started wheezing. And I was like, that's kind of odd. What's going on here. I thought to myself, okay, maybe I'm getting a head cold or something. And then I thought to myself, wouldn't that be funny; I just got the flu shot yesterday; everybody says they end up getting the flu from the flu shot. So I'm like, what's going on here?" *Id.* at 15. Petitioner confirmed that that she distinctly remembered her wheezing began the day after her vaccination. *Id.*

Following the wheezing, Petitioner testified that "a day or two" later, she was getting out of breath after walking multiple flights of stairs. Tr. at 16. The same day, she also developed a cough. *Id.* Then "two weeks later", she developed nasal congestion which lasted "one-two weeks". *Id.* When the congestion disappeared in late November, she still "had the wheezing, the coughing, the shortness of breath. And that continued, so [she] ended up seeing [her] primary care doctor." *Id.* at 16-17. Petitioner testified that during this time, she experienced no fever. *Id.* at 16.

Petitioner testified she saw Dr. Jill Nye on November 29, 2014. *Id.* at 17; *see also* Ex. 49 at 1. She was prescribed Proair, but she testified that her condition continued to worsen. *Id.* at 18. Petitioner testified that two days later (December 1, 2014), she was in the shower and "just couldn't breathe," so she went to the hospital. *Id.* at 19. At the hospital, Petitioner's medical records indicated that her symptoms began "three or four weeks prior or a few weeks ago." *Id.* at 19. This placed onset of Petitioner's symptoms later than she originally had described at her November 29, 2014 visit. Petitioner explained that she "just made a mistake…. I just goofed with the estimate. But I do know it was the day after I had the flu shot because I specifically remember that day." *Id.* at 19.

Petitioner testified that at the hospital, she was feeling out of breath and had to be placed on oxygen right away. Tr at 19. Doctors felt as if Petitioner had "some type of virus and that within a few weeks that [she] should start feeling better." *Id.* at 20.

Petitioner did not feel better and testified that she saw a pulmonary specialist (Dr. Simonelli) on December 14, 2014. Tr. at 20. Dr. Simonelli's notes stated that "Petitioner received a flu vaccine in October at CVS and noticed a slight wheeze since getting the injection. She started with the head cold symptoms one to two weeks prior to Thanksgiving and shortness of breath got progressively worse." *Id.* at 21. Petitioner stated that this generally tracked with her recollection. *Id.* Petitioner stated that Dr. Simonelli believed that the cause of Petitioner's symptoms could have been mold, but didn't know for sure. *Id.* at 22.

Dr. Simonelli's notes also indicated that Petitioner was suffering from reflux at the time. *Id.* at 23. Petitioner testified that this was likely during the time she was taking prednisone and she currently did not suffer from reflux. *Id.*

Petitioner testified that she was still feeling the same symptoms when she underwent a lung biopsy in February 2015. Tr. at 24. The biopsy showed that Petitioner had permanent lung damage and that the only hope she had was a lung transplant. Tr. at 25. It was after the lung biopsy that Petitioner was first diagnosed with bronchiolitis obliterans. *Id.*

Petitioner next testified that she met with University of Pennsylvania physicians in May 2015 to assess her eligibility for a lung transplant. *Id.* at 26. Petitioner was placed on the transplant list, but when her fiancé died in April of 2017, she was removed, as he had been listed as her primary caregiver for care after the transplant. Tr. at 27. Petitioner testified that she currently was not on the transplant list, as the cost and time of aftercare was something she could not afford. *Id.* at 28-29. In addition, evaluations would have to be "redone" to redetermine eligibility. Tr. at 30.

Petitioner testified that at the time of initial diagnosis, she was "on constant oxygen." Tr. at 29-30. She testified that she is "doing better now than [she was] a couple years ago" and only needs oxygen for three to four hours per day. *Id.*

Lastly, Petitioner stated that when she saw any doctors she would "respond to the questions and give [her] histories to the best of [her] ability at that time." Tr. at 31.

IV. Expert Opinions

A. Petitioners' Expert: Dr. Eric Gershwin

Dr. Gershwin provided two expert reports in this case and testified at the entitlement hearing. Ex. 20 (hereinafter "First Gershwin Rep."); Ex. 32 (hereinafter "Second Gershwin Rep.").

1. Qualifications

Dr. Gershwin received his medical degree from Stanford University in 1971 and is board certified in internal medicine, rheumatology, and allergy and clinical immunology. Ex. 38

(hereinafter "Gershwin CV") at 1-2. He is currently the Jack and Donald Chia Professor of Medicine and a Distinguished Professor of Medicine the University of California, Davis. *Id.* at 2. Dr. Gershwin has won numerous awards including a Doctor of Philosophy Honoris Causa from the University of Athens, for his contribution in immunology and medicine, and is the Professor Henry N. Neufeld Memorial Award from the United States-Israel Binational Science Foundation in 2014. *Id.* at 1. Dr. Gershwin has ten patents and serves as the editor-in-chief for Clinical Reviews in Allergy, Reviews in Autoimmunity, Autoimmunity Reviews, and Journal of Autoimmunity, as well as an ad hoc editor for numerous other publications. *See id.* at 5-7. Dr. Gershwin has published more than 900 papers, 162 book chapters, and 69 books/monographs. *See id.* at 8-12, 13-91, 92-106.

2. Dr. Gershwin's First Expert Report

Dr. Gershwin describes bronchiolitis obliterans as follows:

> Bronchiolitis obliterans is essentially a disease of small airways that is histologically associated with constrictive bronchiolitis. Under the microscope, there is narrowing of the luminal area with significant scarring, including the presence of fibrosis. Ultimately, there is a complete destruction of the bronchioles by these fibrotic events, but, interestingly, the alveoli are not affected. In other words, it is a disease of the air tubes. The etiology of this disease is essentially idiopathic. There is presumably an environmental agent, which leads to inflammation and that inflammation ultimately ends up with fibrosis. Interestingly, in the natural history of bronchiolitis, it is assumed that there will be some patients who have epithelial inflammation that end with scarring, but there are others that will end with healing or resolution. Bronchiolitis obliterans has been associated with inhalation injuries such as toxic fumes, with viral infections, with reactions to a variety of drugs, with hematopoietic cell transplantation, and with a number of rheumatic diseases, including rheumatoid arthritis. It is part of the overall syndromes which come under the generic heading of 'bronchiolar diseases' and there may well be significant overlap with a number of these disorders of pulmonary pathology (1-5).

First Gershwin Rep. at 2; *citing*, Devakonda et al., *Bronchiolar disorders: A Clinical-Radiological Diagnostic Algorithm*. 137 CHEST 4, 938-51 (2010) (filed as Ex. 21); Papiris et al., *Bronchiolitis: adopting a unifying definition and a comprehensive etiological classification*, 7 EXPERT REV RESPIR MED 3, 289-306 (2013) (filed as Ex. 22); Devouassoux et al., *Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis*. 33 EUR RESPIR J 5, 1053-61 (2009) (filed as Ex. 23); Barker et al., *Obliterative bronchiolitis*, 370 N ENGL J MED 19, 1820-28 (2014) (filed as Ex. 24); J.F. Cordier, *Challenges in pulmonary fibrosis • 2: Bronchiolocentric fibrosis*, 62 THORAX, 638-49 (2007) (filed as Ex. 25).

Dr. Gershwin opined that Ms. Antalosky had an underlying viral infection and that this viral infection would otherwise have been benign were it not for the concurrent immunization with the seasonal flu vaccine. First Gershwin Rep. at 3.

Dr. Gershwin does not believe that the influenza vaccination alone led to Ms. Antalosky's bronchiolitis obliterans. First Gershwin Rep. at 3. According to Dr. Gershwin, Petitioner had an underlying viral infection that caused initial bronchial inflammation and swelling of her airways as evidenced by the symptomatic wheezing at the time of her vaccination. *Id.* Dr. Gershwin opined that the influenza vaccination then triggered bystander cells which caused further inflammation in the lungs "akin to pouring fuel on a simmering flame in her bronchi[o]ls" *Id*.

Dr. Gershwin explained that the cytokine pathways and signal activation that occur in bronchiolitis obliterans are similar to what one would expect following the immune response to a seasonal influenza vaccine. First Gershwin Rep. at 3. Ms. Antalosky's underlying viral infection triggered an innate immune response and inflammation within her lungs. *Id*. Dr Gershwin stated the mechanism by which Petitioner developed bronchiolitis obliterans as follows: the influenza vaccination triggered the production of cytokines to mediate the immune response to the vaccine, which in turn caused swelling of regional lymph nodes by bystander cells, which led to the production of more cytokines in the lungs resulting in a chronic perpetuation of an immune response. *Id*.

3. Dr. Gershwin's Second Expert Report

At the outset, Dr. Gershwin noted that there are no specific differences of opinion among himself, Dr. Byers and Dr. Bardana regarding Ms. Antalosky's diagnosis or the chronology of events within her medical records.

Dr. Gershwin noted Dr. Bardana's comment, "the virus causing the infection was never identified but very probably was the agent that led to her constrictive bronchiolitis obliterans later"; however, according to Dr. Gershwin, Dr. Bardana offers no data or mechanism of action of how a viral infection may produce bronchiolitis obliterans. Second Gershwin Rep. at 2.

In response to Dr. Byers and Dr. Bardana, Dr. Gershwin stated that there is no reason to conclude that Ms. Antalosky is unreliable in placing the onset of her wheezing one day post-vaccination. Second Gershwin Rep. at 2. He further opined that bronchiolitis obliterans is a rare disease, and therefore stated that epidemiologic analysis of such a rare event is impossible. *Id*. at 2. Dr. Gershwin cited to the Brodin article to show the enormous variation in the human immune system including individual responses to vaccination. *Id*. at 2; Brodin et al., *Variation in the human immune system is largely driven by non-heritable influences*, 15 CELL 160(1-2), 37-47 (2015) (filed as Ex. 33) (hereinafter "Brodin"). Dr. Gershwin opined that Brodin "illustrates how seemingly serendipitous events can lead to a broad influence on immune regulation." *Id*.

Dr. Gershwin discussed "the intense inflammatory response that occurs following influenza vaccination and that significant levels of cytokines are produced within hours which have profound influences on immunity." Second Gershwin Rep. at 4; Chatziandreou et al., *Macrophage Death following Influenza Vaccination Initiates the Inflammatory Response that Promotes Dendritic Cell Function in the Draining Lymph Node*, 18 CELL REPORTS, 2427-40 (2017) (filed as Ex. 38). Dr. Gershwin also noted that neither Dr. Byers nor Dr. Bardana addressed the issue of bystander activation. *Id*. at 4. Dr. Gershwin cited to the Ehl article to illustrate how viral persistence, molecular mimicry and bystander activation may initiate immune reactivity

leading to inflammation. *Id*.; Ehl, et al., *Bystander Activation of Cytotoxic T Cells: Studies on the Mechanism and Evaluation of In Vivo Significance in a Transgenic Mouse Model*, 185 J. EXP. MED. 7, 1241-51 (1997) (filed as Ex. 39) (hereinafter "Ehl").

In summary, Dr. Gershwin further opined that lack of reported cases of influenza vaccine-induced constrictive bronchiolitis is not grounds to argue that no such association exists, and he reminds the Court that" systematic analysis of an individual's T cell responses is not yet possible and illustrates why the rare individual, such as Lisa Antalosky, can develop bronchiolitis obliterans following an influenza vaccination and her own individual pulmonary microenvironment." Second Gershwin Rep. at 5, *citing*, Lever et al., *Architecture of a minimal signaling pathway explains the T-cell response to a 1 million-fold variation in antigen affinity and dose*, 113 PROC NATL ACAD SCI U S A 43, E6630-E6638 (2016) (filed as Ex. 42); Linus Backert & Oliver Kohlbacher, *Immunoinformatics and epitope prediction in the age of genomic medicine*, 7 GENOME MED 119 (2015) (filed as Ex. 43).

4. Dr. Gershwin's Testimony

Dr. Gershwin testified at the February 20, 2020 entitlement hearing. I recognized Dr. Gershwin as an expert in the field of immunology. Tr. at 40. Dr. Gershwin testified that he believed that the flu vaccination that Petitioner received on October 15, 2014, was the but-for cause of her developing bronchiolitis obliterans. *Id.* at 41. Dr. Gershwin testified that following the vaccination, Ms. Antalosky produced cytokines, which caused a bystander effect, or stimulation of immune cells that are typically normal, but in this case, moved to her lungs where there was some ongoing inflammation. *Id.* at 42. The introduction of the cytokines to the ongoing inflammation led to a chronic disease or autoinflammation that led to the development of Petitioner's severe lung disease. *Id.* at 42-43. Petitioner's symptoms of wheezing, coughing, and nasal symptoms were indicative of an acute respiratory infection. *Id.* at 45, 53.

Dr. Gershwin provided a brief description of bronchiolitis obliterans. Tr. at 50-51. Some known causes of bronchiolitis obliterans include inhalation of certain fumes, connective tissue disease like rheumatoid arthritis, and lung transplants. *Id.* at 51.

Dr. Gershwin testified it was speculative as to what kind of viral infection Ms. Antalosky had. Tr. at 53. In this case, Ms. Antalosky already had local cytokines produced in the lungs because of the ongoing viral infection. *Id.* at 55. However, sometimes too much of an immune response produces too much inflammation, and doctors will manually remove the inflammation through aspiration with a large needle, in the example of a joint. *Id.* at 56. Too much inflammation can be harmful and a term experts in the field have used to call it is "autoimmune inflammation" or "autoinflammation". *Id.*

The flu vaccine causes cytokines to be produced and circulated in the sera. Tr. at 58. Cytokines are released from the regional lymph node, in this case the shoulder and eventually end up in the blood or lymphatic system. *Id.* As an example, Dr. Gershwin stated that if a person got a splinter in the finger, cytokines travel from anywhere in the body to the site where an immune response is needed, in this case the finger, and cause inflammation in the finger. *Id.* at 58-59. In this case, Ms. Antalosky had an ongoing viral infection in her lungs and the inflammatory

cytokines, such as TNF-alpha, IL-6, and IL-10, produced by the flu vaccine traveled to the lungs, where they were most needed. *Id.* at 60-62. Autoreactive cells trafficked to Petitioner's lungs and started a "nonreversible cascade" that resulted in chronic lung disease. *Id.* at 63. In a normal person, the flu vaccine would be engulfed by macrophages and dendritic cells, which are then taken to a lymph node. *Id.* at 63-64. The macrophages and dendritic cells present the cells to T and B lymphocytes that produce T and B cells to fight the influenza virus. *Id.* at 64. Because there was a more urgent immune need in Petitioner's lungs, the stimulated T and B cells traveled there and caused a "more potent inflammation." *Id.* at 65.

In the Suwara article, unresolved inflammation leads to the production of oxidants which can "punch holes, lead to scarring." Tr. at 69. These oxidants are called reactive oxidative species (ROS) and ROS are released from neutrophils and macrophages. *Id.* Petitioner's biopsy revealed macrophages, which is evidence of ROS. *Id.* Dr. Gershwin opined that there was clear dysregulation in the repair process, which is evidenced by the fact that Ms. Antalosky did not get better. *Id.*

Dr. Gershwin referenced the Maurice article, which demonstrated that a vaccine induced a systemic inflammatory immune response strong enough to induce bystander activation. Tr. at 71.

Regarding the timing, Dr. Gershwin testified that had Petitioner received the flu vaccine a week before the viral infection, she would not have had this chain reaction. Tr. at 74. It was precisely because the viral infection occurred within a day or two of the vaccine that she developed her injury. *Id.*

Dr. Gershwin testified that the flu vaccine is very safe and recommends it to all of his patients. Tr. at 76. Dr. Gershwin identified Ex. 60 as a case study in which a person developed chronic lung disease after vaccination. *Id.* at 77. Dr. Gershwin also opined that a person's immune response is not entirely based on genetic factors; a study comparing the immune response of identical twins to nonidentical twins showed enormous variance. *Id.* at 78.

Dr. Gershwin testified that he saw one to two patients with bronchiolitis obliterans per year and primarily as a result of rheumatoid arthritis. Tr. at 82. Dr. Gershwin also confirmed that he was involved with the diagnosis, but not treatment of such patients. *Id*. at 83.

Dr. Gershwin stated that he does not believe the T cell process that occurs in lung transplantation cases is the one that occurred with Ms. Antalosky. Tr. at 89-90. Additionally, Dr. Gershwin stated that some vaccines are more potent than others, but the flu vaccine is formulated every year to create a "rigorous production of cytokines." *Id.* at 94.

I asked Dr. Gershwin what specifically made him believe that the combination of the vaccine and virus, and not just the virus, caused Petitioner's condition. Tr. at 98. Dr. Gershwin stated that Petitioner, and millions of others, have viral infections, and those infections do not cause bronchiolitis obliterans; it is a very rare condition. *Id.* Her symptoms of wheezing and nasal congestion did not resolve and only got worse after vaccination. *Id.* at 98-99. Petitioner's symptom of wheezing appeared after vaccination but wheezing is not a post-vaccination symptom, so it must

have been a virus. *Id.* at 99. Bystander activation would start within days and continues to become exacerbated and the effects become uncontrolled. *Id.* at 100.

B. Respondent's Expert: Dr. Derek Byers

Dr. Byers provided two expert reports in this case and testified at the entitlement hearing. Ex. A (First Byers Rep.), Ex. E (Second Byers Rep.).

1. Qualifications

Dr. Byers received a B.S. in Microbiology from the University of Oklahoma in 1993. Ex. B (hereinafter "Byers CV") at 1. He received a Ph.D. in immunology from the UT Southwestern Graduate School in 1999 and completed medical school at the University of Texas Southwestern Medical School in 2001. Byers CV at 1. He completed an internship at UT Southwestern in Internal Medicine in 2002 and served as a resident in the same program from 2002-2004. *Id.* He served as the chief resident from 2004-2005, and from 2005-2008 completed a fellowship at Washington University in St. Louis School of Medicine in Pulmonary and Critical Care Medicine. *Id.* at 2. From 2007-2009, Dr. Byers conducted research into the characterization of immune cells and cytokines involved in IL-13-mediated chronic airway disease. *Id.* Dr. Byers was also a Postdoctoral Research Appointee in the Division of Pulmonary/Critical Care at Washington University School of Medicine in 2010. *Id.*

Dr. Byers was an Assistant Professor of Medicine at Washington University from 2010-2016. Byers CV at 2. Dr. Byers currently serves as an Associate Professor of Medicine, the Director of Pulmonary Morphology Core, Division of Pulmonary and Critical Care Medicine at Washington University School of Medicine, as well as the Associate Fellowship Program Director for Research. *Id.* He holds numerous university, hospital, and committee appointments. *Id.* He serves on several editorial boards for academic journals and holds memberships in four professional organizations. *Id.* at 3-5. He has received numerous research awards specifically targeted to lung research and has conducted several clinical trials. *Id.* at 6-8. He also has co-published eighteen articles and has written several abstracts. *Id*. at 11-12.

Dr. Byers is licensed to practice pulmonary disease and critical care medicine by the American Board of Internal Medicine and the State of Missouri Physicians and Surgeons. Byers CV at 3.

2. Dr. Byers' First Expert Report

Dr. Byers agreed with Dr. Gershwin that an upper respiratory tract infection contributed to the development of Ms. Antalosky's severe lung disease. First Byers Rep. at 3. However, Dr. Byers stated that Ms. Antalosky's lung disease more likely developed "by inhaled exposure to a respiratory virus plus an inhaled allergen or inhaled irritant of some type that led to progressive airway-focused lung disease," and that her "mycobacterial lung infection contributed to her overall illness, based on the improvement in symptoms that she experienced after treatment with the multi-antibiotic regimen." *Id.*

Dr. Byers opined that Dr. Gershwin's theory is flawed because the medical records do not support Petitioner's affidavit stating that her wheezing began the day after her vaccination. First Byers Rep. at 2; Ex. 11 at 1. The contemporaneous medical records indicate that Petitioner first experienced wheezing a few weeks after her vaccination in mid-November of 2014. First Byers Rep. at 2. Thus, according to Dr. Byers, Petitioner was likely not suffering from a viral infection at the time she was vaccinated.

Dr. Byers also argued that Dr. Gershwin failed to provide reliable evidence to explain how an intramuscular flu shot in the arm could lead to a progressive airway-based lung disease. First Byers Rep. at 5. He also considered Dr. Gershwin's statement that "her disease would have otherwise been reversible had she not received this vaccination to be "mere speculation and unfounded." *Id*. Dr. Byers did not find any medical literature reporting cases of influenza vaccine-induced constrictive bronchiolitis or bronchiolitis obliterans and "no evidence that an influenza vaccination could cause or worsen these types of lung disease." *Id*. at 4.

Dr. Byers did not find the case studies submitted by Dr. Gershwin to be persuasive because the clinical course of the seven patients identified as developing interstitial lung disease following influenza vaccination was much different than that of Petitioner. First Byers Rep. at 4. For example, four had a history of prior lung disease, six were characterized by fever, and all seven developed symptoms within one week of vaccination and responded to treatment with steroids. *Id*. In contrast, Petitioner did not have a fever. *Id*. Her symptoms did not fully develop until six weeks after vaccination, and she did not respond to treatment with steroids. *Id*. at 4-5. Regardless, according to Dr. Byers, the case reports submitted by Dr. Gershwin do not establish that the influenza vaccination actually caused the subject patients to develop interstitial lung diseases. *Id*.

In support of his own theory, Dr. Byers stated that [s]everal respiratory viruses have been linked to the development of bronchiolitis obliterans, the most common being rhinoviruses/enteroviruses, parainfluenza viruses (including respiratory syncytial virus, parainfluenza viruses, human metapneumoviruses), and coronaviruses, with influenza suggested in fewer cases. First Byers Rep. at 3; Fisher et al., *Symptomatic Respiratory Virus Infection and Chronic Lung Allograft Dysfunction*, 62 CLIN INFECT DISEASE 3, 313–19 (2016) (filed as Ex. A2). Dr. Byers stated that although Petitioner's viral testing came back negative on December 1, 2014, that testing was not performed until several weeks after her respiratory symptoms began and after the virus had already resolved. *Id.* at 3-4. Thus, testing was too late "to identify the virus that infected her upper respiratory tract and led to her symptoms in early-mid November 2014." *Id*.

Dr. Byers claimed that Petitioner also had several risk factors for airway diseases prior to her vaccination including prior episodes of bronchitis, pneumonia, URIs that warranted medical care, and a predisposition for inflammatory conditions as evidenced by her irritable bowel syndrome, her low-positive ANA, and an unusual episode of swelling that involved her legs, face, and vaginal area with associated culture-negative urinary tract infection between June and August of 2013. First Byers Rep. at 4, *citing*, Ex. 19 at 204. Dr. Byers stated that even Dr. Simonelli noted her clinical predisposition to develop bronchiolitis as a "diathesis to airways disease" on December 17, 2014. *Id*, *citing*, Ex. 4 at 18. In light of her predisposition, Dr. Byers argued that "Dr. Gershwin's cytokine hypothesis provides insufficient mechanistic plausibility for how an

influenza vaccination in the arm could have led to Ms. Antalosky's airway-focused, irreversible lung disease." *Id.*

Dr. Byers also highlighted that "The American Thoracic Society, Centers for Disease Control and Prevention, World Health Organization and other healthcare societies unanimously recommend influenza vaccinations for people with severe chronic lung diseases, including native lung constrictive bronchiolitis and transplant-associated bronchiolitis obliterans. First Byers Rep. at 4, *citing*, Niederman et al., *Guidelines for the Management of Adults with Community-acquired Pneumonia: Diagnosis, Assessment of Severity, Antimicrobial Therapy, and Prevention*, 163 AM J RESPIR CRIT CARE MED. 7, 1730-54 (2001) (filed as Ex. A6); Grohskopf et al., *Prevention and Control of Seasonal Influenza with Vaccines*, 65 MMWR RECOMM REP 5, No. RR-5, 1–54 (2016) (filed as Ex. A7); *Vaccines against influenza WHO position paper*, 23 WKLY EPIDEMIOL REC. 8, 461-76 (filed as Ex. A8).

In sum, Dr. Byers does not believe that the flu vaccine contributed to the irreversible pathogenesis of Petitioner's disease process. First Byers Rep. at 3.

3. Dr. Byers' Second Expert Report

In response to Dr. Gershwin's supplemental report, Dr. Byers noted that Dr. Gershwin provided no additional evidence demonstrating the mechanism by which the influenza vaccine can lead to severe lung disease. Second Byers Rep. at 1. "Dr. Gershwin resorts to rank speculation to suggest that maybe, just maybe, the vaccine on 10/12/2014 led to a series of 'serendipitous events' that affected Ms. Antalosky's normal immunoregulatory mechanisms to result in irreversible lung disease." *Id.*

Dr. Byers noted that although Dr. Gershwin cited to literature laying out the fundamental principles of immunology, he failed to provide any explanation for how those basic tenets can result in a dysregulated immunologic response resulting in severe irreversible lung disease. Second Byers Rep. at 1. Dr. Byers also pointed out that none of the fundamental literature involved the influenza vaccine. *Id.*

Upon conducting another search, Dr. Byers "found no new case reports or animal models that provide evidence that the influenza vaccine has a causal relationship to the development of lung disease. Second Byers Rep. at 1. In contrast, Dr. Byers reported that "thousands of patients have undergone lung transplantation since the late 1980s, and still developed fulminant bronchiolitis obliterans while taking intense immune suppressive therapies that block immune cell activity," and that "[h]undreds of millions of patients have had flu vaccinations, including patients with severe constrictive bronchiolitis, obliterative bronchiolitis, mycobacterial lung diseases, and other severe chronic lung diseases" with no reports of an adverse effect such as that theorized by Dr. Gershwin. Second Byers Rep. at 3. Dr. Byers reiterated that it "much more likely that a respiratory virus infection that [Ms. Antalosky] acquired in September-October 2014 contributed to the airway disease that she sustained, *independent* of the flu vaccination. *Id.*

With respect to bystander activation, Dr. Byers noted that the theory was vaguely mentioned in Dr. Gershwin's first report, and that, by Dr. Gershwin's own admission, "the

mechanisms by which inflammation influences the adaptive immune response to vaccines is not fully understood." Second Byers Rep. at 2. Dr. Byers further pointed out that the Zinkernagel article found that bystander activation "is usually not of major biologic consequence." *Id*. Dr. Byers remarked: "How bystander activation that is induced by a flu vaccine would lead to an airway-centric lung disease that did not afflict any other part of [Ms. Antalosky's] body is illogical to me based on what is known to occur." *Id*.

Finally, Dr. Byers noted that he has not ignored the chance that uncommon events may occur; however, "the validity of Dr. Gershwin's hypothesis extends beyond the chance of an uncommon event occurring." Second Byers Rep. at 3. "Truthfully, Dr. Gershwin is the first and only physician I have encountered that is convinced that a flu vaccine may cause this type of irreversible lung disease, so his views on this matter do not reflect those of the general medical community." *Id.* at 2.

4. Dr. Byers' Testimony

Dr. Byers also testified at the February 20, 2020 entitlement hearing. I recognized Dr. Byers as an expert in pulmonology with expertise in immunology. Tr. at 113. Dr. Byers testified that he does not believe the flu vaccine contributed to Petitioner's chronic lung disease. *Id.* at 115. Dr. Byers stated that pulmonologists would agree that constrictive bronchiolitis is a result of direct airway injury following some sort of inhaled injury to the lung. *Id.* Known causes of constrictive bronchiolitis include inhaling chemicals like diacetyl, mustard gas, smoke, GERD, and respiratory viral infections. *Id.*

Dr. Byers testified that bronchiolitis obliterans is more of a clinical disease whereas constrictive bronchiolitis is the pathologic identification of the disease, and bronchiolitis obliterans syndrome is a disease that can occur in transplant recipients. Tr. at 117. The deterioration of the lungs takes weeks to months and is an irreversible process. *Id.*

Dr. Byers recommends all of his patients with chronic lung disease receive the flu vaccine. Tr. at 123. If Dr. Gershwin's theory of bystander activation were to occur, any vaccination given to a lung transplant patient would induce rejection. *Id*. at 124. Transplanted lungs have major histocompatibility differences that activate T cells all the time, which could lead to rejection, so lung transplant patients receive medications that block T cell activation and lymphocyte proliferation. *Id.* at 124-25. In a study done with future lung transplant donors, samples are collected from their nasal passages and airways through a bronchoscopy, and at any given time, 20% of the donors have a virus in their lower or upper respiratory tract and many of them did not have any symptoms. *Id.* at 127-28. If Dr. Gershwin's theory regarding bystander activation were true, we should expect to see more cases of autoinflammation. *Id.* at 128.

Dr. Byers added that Ms. Antalosky's negative PCR test of December 1st did not confirm that she did not have a viral infection, just that the test did not result in the confirmation of one. Tr. at 128-29. There could have bad swabbing or the PCR test was too sensitive to produce a result. *Id.* Additionally, a nasal swab might not detect a viral infection, where a bronchoscopy in the lower airways might have. *Id.* at 129. Dr. Byers confirmed that he believes that Petitioner had a viral infection in the six to eight week window between when she received her vaccine and when she

was tested. *Id.* at 130. There is no medical literature linking bystander activation and constrictive bronchiolitis, however Dr. Byers believes the concept is a "very reasonable explanation for why localized inflammation may occur," and "could have been very well been occurring with the acute respiratory viral infection that she had that corresponded to the time with her vaccination." *Id.* at 134. Dr. Byers clarified that he did not believe that bystander activation triggered by the influenza vaccine would be "any greater than what occurred with an active virus infection" and the influenza vaccine does not produce a robust immune response that lasts your lifetime, which is why we need a new vaccination every year. *Id.* at 135.

Dr. Byers maintained that a direct attack occurred in Ms. Antalosky's airways, be it a viral infection or a chemical. Tr. at 136-37. The flu vaccination Petitioner received would not have been a direct attack on her lungs. *Id.* at 137. Petitioner's ongoing viral infection led to "an immune response that went bad or a healing response that went bad and led to the irreversible fibrosis that she endured." *Id.* The vaccination was chronologically related but has nothing to do with causation. *Id.* at 137-38. Ms. Antalosky had no symptoms to indicate she had a reaction to the vaccine; she had no fever, redness at the injection site or any other manifestations of a profound inflammatory response. *Id.* at 138. The active respiratory virus infection is much more of an inflammatory stimulus that a vaccination. *Id.* at 139-40, 143. In the literature that Dr. Gershwin cites, cytokine levels did increase after vaccination but returned to the baseline within 48 hours. *Id.* at 143. People who have an active viral infection in their airways have symptoms that last for days, and have an immune response that is much more significant that the cytokine increase following a vaccination. *Id.* at 144.

Dr. Byers also testified regarding Petitioner's biopsy. Tr. at 146-48. The biopsy indicated Ms. Antalosky had a lot of inflammation, and she sustained an epithelial injury. *Id.* at 147. The biopsy also did not indicate she had vasculitis, which would be suggestive of an autoimmune condition. *Id.* at 147-148.

Dr. Byers testified that only mouse models have identified bystander activation; to extrapolate those findings to humans in the context of lung disease "is a bit of a stretch." *Id.* at 153-54. Dr. Byers opined that Ms. Antalosky's clinical course was consistent with someone who developed constrictive bronchiolitis following an upper respiratory infection. *Id.* at 156. Dr. Byers was asked whether he would vaccinate a patient with an active viral illness and stated that he would not if they were acutely ill, however the default at his place of employment is to give everyone the flu vaccine, especially from September through December. *Id.* at 163-64. The main issue with Dr. Gershwin's theory of causation is the idea of bystander cells from an axillary lymph node drive a process in the lungs. *Id.* at 167.

C. Respondent's Expert: Dr. Emil Bardana

Dr. Bardana provided two expert reports in this case. Ex. C (hereinafter "First Bardana Rep."), Ex. F (hereinafter "Second Bardana Rep.").

1. Qualifications

Dr. Bardana received a double B.S. in Biology and Philosophy from Georgetown University in 1957. Ex. D at 1 (hereinafter "Bardana CV"). He completed medical school at McGill University (Canada) in 1961 and an internship in straight medicine in 1962. Bardana CV at 1. Dr. Bardana served as an internal medicine resident from 1965-1968 (chief resident from 1967-68) at Oregon Health Sciences University. *Id.* at 1-2. He served as a research and clinical fellow in the Division of Immunology, Allergy and Rheumatology at OHSU from 1968-69, and as a research trainee from 1969-1971 in the Department of Allergy and Clinical Immunology at the University of Colorado Health Sciences Center. *Id.* at 2. Dr. Bardana served in the military as a military doctor from 1962-1965. *Id.*

Upon returning from Vietnam, Dr. Bardana held numerous academic appointments at Oregon Health & Science University, eventually serving as the Head, Division of Allergy and Clinical Immunology. Bardana CV at 2. Dr. Bardana retired as Professor Emeritus in 2014. *Id.* at 3.

Dr. Bardana is licensed to practice in allergy and immunology in both Oregon and Washington. Bardana CV at 4. He holds numerous professional society memberships and has received many honors and awards. He has served on numerous boards in various capacities and has served on the board of three academic journals related to the research of allergy and immunology. *Id.* at 11. He holds dozens of committee appointments and has been invited to deliver lectures at hospitals and universities around the country. *Id.* at 12-14. He has published 61 research publications. *Id.* at 15-40.

2. Dr. Bardana's First Expert Report

Dr. Bardana concurred with Dr. Byers in his opinion that Petitioner's condition was likely the result of a viral infection that was never identified, given the time that passed before viral testing was performed. First Bardana Rep. at 27, 28.

Dr. Bardana regarded Dr. Gershwin's theory as both unproven and unprecedented; that the appearance of a nonspecific symptom such as wheezing within one day of vaccination is not sufficient evidence of causality; and that wheezing does not necessarily reflect inflammation in the lower airways. First Bardana Rep. at 28-29. Moreover, the timeframe as reported by Petitioner regarding the onset of her wheezing is not supported by the contemporaneous medical records. *Id.* at 29.

Dr. Bardana pointed out that Dr. Gershwin cited no literature that directly supports his theory that an immune response to a presumed ongoing viral infection in association with the expected immune response to a vaccination would precipitate a more intense response in the bronchial tissue leading to bronchiolitis obliterans. First Bardana Rep. at 28. Dr. Bardana stated that "[i]n the many millions of vaccine doses that have been administered, there are no published instances that the antigenic immune response to an invading virus agent induced tissue damage which colluded with the vaccine response to result in a heightened destructive process in the lung tissue." *Id.*

In conclusion, Dr. Bardana stated that Dr. Gershwin's theory lacks biologic plausibility and coherence and is completely unsupported by any reliable medical evidence. First Bardana Rep. at 29. It is Dr. Bardana's opinion that the influenza vaccine played no role in Petitioner developing bronchiolitis obliterans. *Id*. at 31.

3. Dr. Bardana's Second Expert Report

Dr. Bardana agreed with Dr. Byer's observation that there are no reported cases of influenza vaccine-induced bronchiolitis obliterans. Second Bardana Rep. at 2. In light of the nearly 500 million influenza vaccines administered between the years 2011 and 2015, Dr. Bardana finds it compelling that not a single case of bronchiolitis obliterans has been reported, especially considering adverse reactions are carefully monitored by national and international organizations. Second Bardana Rep. at 2.

Dr. Bardana did not dispute that the studies submitted by Dr. Gershwin "verify the variability of the human immune response to a diverse group of immunogens"; however, "they do not support Dr. Gershwin's opinion that Ms. Antalosky may have had a subclinical viral infection at the time of her vaccination, manifested by a recalled 'slight wheeze', causing airway inflammation which interacted with her ongoing immune response to the influenza vaccine causing more intense bronchial tissue damage leading to bronchiolitis obliterans." Second Bardana Rep. at 3.

Dr. Bardana stated that there "is an imposing lack of connotation and logic" between the studies cited by Dr. Gershwin and Dr. Gershwin's theory of causation. For example, the Chatziandreou article cited by Gershwin postulates that in murine models "lymph node macrophages are key players in the initiation of the IL-1a-mediated inflammatory response that follows influenza vaccination", and that "stimulation of the IL-1a inflammatory pathway might therefore represent a strategy to enhance antigen presentation and improve the humoral response against influenza vaccines," i.e. c*onfer improved protection*. Second Bardana Rep. at 3 (emphasis added), *citing*, Chatziandreou. Assuming the murine models could be replicated in humans, Dr. Bardana struggled to appreciate how these findings relate to or support Dr. Gershwin's proposed theory of how Ms. Antalosky developed bronchiolitis obliterans. Second Bardana Rep. at 4. Moreover, Dr. Bardana further highlighted that the authors of the Chatziandreou article admit that "the mechanism by which inflammation influences the antibody response to vaccines is unclear." *Id*. at 3, *citing* Chatziandreou at 2427.

With respect to bystander activation, the Zinkernagel study used mouse models to demonstrate how bystander activation may be employed as a pathway by which vaccine ingredients might induce autoimmunity. Second Bardana Rep. at 4. The major issue with respect to Ms. Antalosky's case, according to Dr. Bardana, is that bronchiolitis obliterans is not considered an autoimmune disorder despite the fact that it may manifest as part of the rheumatoid arthritis spectrum." *Id*. Nonetheless, the paper concludes by stating that bystander activation was not sufficient to cause clinically manifest autoimmune disease, and the authors did not find the mechanism to be a major biological consequence. *Id*.

In conclusion, Dr. Byers reiterated that "despite the surveillance that has taken place over the billions of vaccinations with influenza, there is not a single case of bronchiolitis obliterans reported as an adverse response to this type of vaccine." Second Bardana Rep. at 6. Dr. Bardana maintained his opinion that Ms. Antalosky's influenza vaccination did not play any contributory role in the generation of her bronchiolitis obliterans. *Id.*

V. Applicable Law

A. Petitioner's Burden

Under the Vaccine Act, a petitioner may prevail in one of two ways. First, a petitioner may demonstrate that she suffered a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the time period provided in the Table. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed in the Vaccine Injury Table, a petitioner may demonstrate that she suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

For both Table and non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010); *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873* (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records of by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen*. *Althen* requires that petitioner establish by preponderant evidence that the vaccinations he received caused her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation."

Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs.*, 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility … in many cases may be enough to satisfy *Althen* prong one" (emphasis in original)), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish her overall entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, because they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing … that mandates that the testimony of a treating physician is sacrosanct -- that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record -- including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Hum. Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs.*, No. 06-522V 2011 WL 1935813 at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between

the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013). *Koehn v. Sec'y of Health & Hum. Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Law Governing Analysis of Fact Evidence

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs.*, 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras*, 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) *mot. for rev. denied*, 142 Fed. Cl. 247, 251-52 (2019), *vacated on other grounds and remanded*, 809 Fed. Appx. 843 (Fed. Cir. Apr. 7, 2020).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL 6117475 at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony -- especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d

1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475 at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent and compelling." *Sanchez*, 2013 WL 1880825 at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs.*, No. 90-2808V, 1998 WL 408611 at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *LaLonde v. Sec'y of Health & Hum. Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (*citing Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the

theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate persuasiveness and reliability of expert testimony has routinely been upheld. *See*, e.g., *Snyder*, 88 Fed. Cl. at 743. In this matter, (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

D. Consideration of Medical Literature

Finally, although this decision discusses some but not all of the medical literature in detail, I have reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VI. Analysis

Petitioner summarized her theory of the case as follows: In October 2014, Petitioner was

suffering from a mild viral infection. She would have recovered with no complications, but while she was actively suffering from the infection, she was given a flu vaccine. The cytokines created by Petitioner's body in order to respond to the flu vaccine inadvertently responded to the inflammation created by the viral infection, eventually creating a cascading reaction which caused Petitioner's chronic lung condition. Respondent contended that Petitioner's flu vaccine "was irrelevant in the development of her lung disease." Tr. at 125.

A. Bronchiolitis Obliterans Generally

Dr. Gershwin described bronchiolitis obliterans as follows:

> we have air tubes which start up in the trachea and go down, and they bifurcate in the lung. And they are big tubes. The big tubes, like the branches on a tree, begin to get smaller and smaller and ultimately have the bronchioles. And this disease tends to affect the small bronchioles, typically less than a couple mms in thickness.

Tr. at 50. Bronchiolitis obliterans results in injury and inflammation to the small airway epithelial cells. Barker at 820. This leads to excessive fibroproliferation, "due to aberrant tissue repair, including ineffective epithelial regeneration in response to tissue injury." *Id.* Cytokine and chemokine levels have been shown to be elevated in bronchiolitis obliterans associated with lung transplantation. *Id.* at 821.

The experts all agreed that bronchiolitis obliterans is an [e]xceedingly rare condition." (Dr. Byers, Tr. at 114-15). Dr. Byers testified that he only sees one or two cases per year. *Id.* at 121.

Dr. Byers discussed the different terms that had been used throughout the case. He described bronchiolitis obliterans as a clinical disease, while constrictive bronchiolitis is the "pathologic identification of the disease." Tr. at 117. Bronchiolitis obliterans syndrome is a disease that occurs in transplant patients. *Id.*

In describing the pathogenesis of this disease, Dr. Byers testified that "Pulmonologists would agree that constrictive bronchiolitis is a result of direct airway injury that arises following some sort of inhaled injury to the lung." Tr. at 115. He described the example of military members who inhaled smoke from Middle East tar pits who went on the develop constrictive bronchiolitis due to the smoke inhalation. *Id.* Bronchiolitis obliterans can be caused by inhalation of toxic chemicals, viral infections, and autoimmune diseases. Vilchez et al., *Infectious Etiology of Bronchiolitis Obliterans: The Respiratory Viruses Connection - Myth or Reality?*, 3 AMERICAN JOURNAL OF TRANSPLANTATION, 245-49 (2003) (filed as Ex. 12).

Dr. Byers testified that "It's very rare that constrictive bronchiolitis occurs, so it's hard to say why it occurs in some people, why it occurs in so few people but no one else. But it has to do with the direct injury to the lung that leads to the disease process." Tr. at 116.

B. *Althen* Prong One

In the context of the Program, "to establish causation, the standard of proof is

preponderance of evidence, not scientific certainty." *Langland v. Sec'y of Health & Hum. Servs.*, 109 Fed. Cl. 421, 441 (2013). Petitioner's burden under *Althen*'s first prong is to provide a medical theory causally connecting the vaccination and the injury. *Id.* This theory must be sound and reliable. *Boatmon*, 941 F.3d at 1359. Petitioner need not precisely identify a causative mechanism to prove causation in fact as the "identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program." *Knudsen,* 35 F.3d at 543.

Petitioner's theory in the case can be summarized as follows: Petitioner had a viral infection that "caused cellular damage and an innate immune response exposing antigens." Ex. 50 at 11. After vaccination, lung-reactive cells were stimulated via bystander activation and were "propagated in the lymph node or *in situ*." *Id.* Autoreactive cells were then trafficked to the lungs "starting a non-reversible cascade of self-perpetuating events resulting in severe chronic pathology." *Id.*

Petitioner's theory can be broken down into several steps. 1) Petitioner was responding to a sub-clinical viral infection which involved the production of cytokines and chemokines in her respiratory tract); 2) she received a flu vaccination, which caused additional cytokine production; 3) vaccination and viral infection resulted in cytokine-driven bystander activation; 4) bystander T cells trafficked to the lung because they sense there's an injury which leads to further dysregulation and further recruitment of inflammatory cells. Tr. at 72.

1. Both Viral Infection and Vaccination Cause Cytokine Production (Steps 1&2)

Dr. Gershwin noted that first, an active pre-existing viral infection must exist in a patient's lungs prior to vaccination. In order for a reaction between the vaccine and the viral infection to occur, the infection needs to be active at the time of introduction of the vaccine. Tr. at 75. The infection need not be specific, but generally is a respiratory infection such as parainfluenza, rhinovirus, or even coronavirus. *Id.* at 53. Moreover, a reaction leading to chronic lung disease will not happen in all cases, only cases in which a "perfect storm", as Dr. Gershwin describes it, occurs. *Id.* at 86.

Following the detection of a viral infection, the body begins to produce cytokines. Tr. at 55. Similarly, flu vaccination also generates cytokine production. Cytokine production occurs in all patients who receive vaccines in order to mediate an immune response. First Gershwin Rep. at 3. Dr. Gershwin opined that the more potent the vaccine, the higher the production of cytokines will be in a patient. Tr. at 94. The influenza vaccine, Dr. Gershwin stated, results in a "rigorous production" of cytokines. *Id.*

Dr. Gershwin testified that local cytokines are produced in the lung early in a viral infection. Tr. at 55. He further described that these cytokines do not simply remain in the lungs; they spill into lymphatics and into the circulation. *Id.* at 59.

Just as cytokines are released following viral infection, they are also released from a vaccination; this can occur in several ways. Tr. at 58. Cytokines are produced and circulated in the sera. *Id.* They are also produced in the regional lymph nodes (where the vaccine was delivered).

Id. Ultimately, cytokines end up in the bloodstream and will traffic in the body. *Id.* Dr. Byers agreed, testifying as follows: "I believe that influenza vaccine leads to cytokine release that circulates throughout the body." *Id.* at 167.

Steps one and two of Petitioner's theory are well established: both viral infection and vaccination produce cytokines that traffic throughout the body.

2. Bystander Activation (Step 3)

When cytokine production commences in patients with a viral infection, "otherwise irrelevant" cells are activated via a process known as bystander activation. First Gershwin Rep. at 3, *see also* Tr. at 42, 68, 88. Dr. Gershwin defined bystander activation as "the activation of T cells specific for an antigen X during an immune response against antigen Y." Second Gershwin Rep. at 4, *see also* Ehl. In this case, the T-cells designed to be activated to respond to the inflammation caused by the influenza vaccine were actually activated to respond to the pre-existing viral infection in the lungs. Bystander activation can also occur in active viral infections, independent of vaccine introduction. Tr. at 88.

As support for his bystander activation theory, Petitioner filed an article by Robert Fujinami. Fujinami, et al., *Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease*, 19 CLINICAL MICROBIOLOGY REVIEWS 1, 80-94 (2006) (filed as Ex. 40) (hereinafter "Fujinami"). Fujinami described the theory of bystander activation:

> virus infections lead to significant activation of APCs such as dendritic cells. These activated APCs could potentially activate pre-primed autoreactive T cells, which can then initiate autoimmune disease (bystander activation of autoreactive immune T cells). In addition to this mode of bystander activation of autoreactive T cells, virus-specific T cells also might initiate bystander activation. For example, virus-specific T cells migrate to areas of virus infection/antigen such as the heart, pancreas, or central nervous system (CNS), where they encounter virus-infected cells that present viral peptides in the context of MHC human leukocyte antigen (HLA) class I molecules to virus-specific T cells. The $CD8^+$ T cells recognize these infected cells and release cytotoxic granules resulting in the killing or death of the infected cells. Under these circumstances the dying cells, the $CD8^+$ T cells and inflammatory cells (macrophages) within the inflammatory focus release cytokines such as tumor necrosis factor (TNF), TNF-B, lymphotoxin (LT), and nitric oxide (NO), which can lead to bystander killing of the uninfected neighboring cells. This results in additional immunopathology at sites of infection. This also appears to be true for $CD4^+$ T cells that can recognize peptide in the context of class II molecules. Here cytokines released by the $CD4^+$ T cells can directly kill uninfected cells but also macrophages can kill uninfected cells in a bystander manner.

Fujinami at 81.

Although not binding on me, another special master found that bystander activation is a sound and reliable causation theory under *Althen* prong one. *See G.C. v. Sec'y of Health & Hum.*

Servs., 15-773V, 2019 WL 4941087 (Fed. Cl. Spec. Mstr. Sept. 5, 2019) (finding that bystander activation is a reasonable and reputable theory that is recognized in the literature and can explain the role of the vaccine in causing autoimmune vasculitis).

Dr. Byers testified at hearing that he believes bystander activation can occur indicating that it has been proven in mouse models. Tr. at 167. He opined as follows:

> I think the concept of bystander activation is a very reasonable explanation for why localized inflammation may occur. So I think from an immunological perspective, that bystander activation could occur in the setting of respiratory virus infection. She could have had activation locally. She did have activation locally of inflammatory pathways that led to an aberrant healing or inflammatory response in her airways that led to the scarring and fibrosis that she had. So bystander activation could have very well been occurring with the acute respiratory viral infection that she had that corresponded to the time with her vaccination.

Id. at 134. Dr. Byers consistently testified that he believed Petitioner's viral infection was the cause of her condition. With respect to bystander activation, he stated: "I don't believe that the bystander activation that would occur with an influenza vaccine would be any greater than what occurred with an active virus infection." *Id.* at 135. He further testified, "So I think the immune response that occurs at the time of active infection is much more substantial than occurs with the vaccination." *Id.* While it may be true that Petitioner's viral infection generated a more substantial immune response than her vaccination, and further, that the bystander effect from the infection was greater than from the vaccination, these points do not prevent Petitioner from establishing that bystander activation is a sound and reliable theory that led to her development of bronchiolitis obliterans.

3. Trafficking of T Cells (Step 4)

The final step in Petitioner's theory is that these activated T cells trafficked to the lungs and caused persistent and unresolved inflammation. Dr. Gershwin stated that in order to traffic the cells to the lung, a patient's body essentially "senses" inflammation; chemokines in the lung, which detect inflammation are "called to" lymphocytes carrying the activated cytokines, thereby bringing the cells to the lung. Tr. at 68. These cells which "sense" inflammation are known as IL-12 cells. Xin, et al., *A Molecular Threshold for Effector CD8^{+} T cell differentiation controlled by transcription Factors Blimp-1 and T-bet*, 17 NATIONAL IMMUNOLOGY 4, 422-32 (April 2016) (filed as Ex. 51). Dr. Gershwin made it clear that had there not been a viral infection, this trafficking would not have occurred. Tr. at 68.

With respect to the trafficking of T cells, Dr. Gershwin testified as follows:

> How do they know to migrate there? Well, we have other molecules called chemokines, and they are like magnets. So when there's inflammation going on in the lung, the chemokine receptors become … upregulated, and that serves as a magnet to lymphocytes, for example, following the vaccination, who have chemokines on their surface. As they go around the body, they sense that there is a

> chemokine receptor that needs them, and that's how the body, how it knows to traffic or to go where it's supposed to go…

Tr. at 68.

Dr. Byers opined that the trafficking of these activated T cells to the lung is merely a hypothesis. Tr. at 166.

In support of this aspect of their theory, Petitioner cited to an article by Nicholas Maurice. *See* Maurice et al., *CXCR3 enables recruitment and site-specific bystander activation of memory CD8⁺ T cells,* 10 NATURE COMMUNICATIONS 4987, 1-15 (2019) (filed as Ex. 52) (hereinafter "Maurice"). Studying samples from a human vaccine trial, the authors followed up on evidence suggesting bystander activation of memory $CD8^+$ T cells occurs soon after vaccination. Maurice at 2. Through their use of a mouse model, they found that "bystander activation during localized inflammation hinges on the ability of memory $CD8^+$ T cells to rapidly migrate to sites of early immune activation in a CXCR3-dependent manner." *Id.* The authors deduced the following:

> [B]ased on these data, we concluded that the [intramuscular] vaccine either elicited a systemic inflammatory immune response strong enough to induce bystander activation or, alternatively, it could indicate that there was localized bystander activation in the draining lymph nodes followed by release of the bystander-activated T cells to the periphery.

Maurice at 8-9. Dr. Gershwin testified that the Maurice article demonstrates that the bystander-activated T cells can leave the lymph nodes and travel throughout the body. Tr. at 71.

Dr. Byers commented on the Maurice article, noting that it is a mouse model that is not founded in humans. Tr. at 170. Dr. Byers called the theory a "stretch" in terms of driving pathology. *Id.* at 170. He opined that it is "premature to implicate bystander activation based on the mouse models that identify this bystander activation being pathologic in the development of lung disease." *Id.* at 155.

While the Maurice article did not conclude that bystander activation resulted in pathology, I do not find this level of scientific certainty and specificity is required in order for Petitioner to meet her prong one burden.

As part of this final step in her theory, Petitioner opined that the process becomes cascading. The cells called to fight the inflammation in the lung do even more damage to the lung. This in turn causes more cells to traffic to the injury, which then leads to further dysregulation of the healing process. Eventually, the dysregulation became too great, and the patient is left with a chronic lung injury. Tr. at 69. Dr Gershwin testified as follows:

> So ultimately the cytokines produced in the lung, including production by the respiratory epithelium itself, by the lymphocytes which are there, basically cannot be controlled. It becomes unresolved inflammation, a persistent autoinflammation,

> and that leads to production of oxidants. Oxidants will punch holes, lead to scarring. The oxidants are often called ROS or reactive oxidative species...

Id.

Petitioner cited the Suwara article in support of this proposition. Suwara et al., *IL-1α released from damaged epithelial cells is sufficient and essential to trigger inflammatory responses in human lung fibroblasts*, 7 MUCOSAL IMMUNOLOGY 3, 684-93 (2013) (filed as Ex. 55) (hereinafter "Suwara"). Suwara noted that,

> In chronic lung disease where there is dysregulation of repair processes resulting in failure to fully resolve inflammation, further bystander tissue damage can result from the cytotoxic properties of soluble proteases and reactive oxygen species released from activated neutrophils and macrophages. This chronic response can lead to the development of fibrosis, characterized by intensive fibroproliferation and activation of airway or parenchymal fibroblasts.

Suwara at 684. The Suwara article provides some evidence that the bystander process can become a "chronic response" that results in persistent/chronic lung disease.

The Maurice paper also discussed persistent activation in noting as follows: "Thus, bystander-activated T cells appear to be a double-edged sword with benefits for the host when activation is brief … and detrimental when activation is persistent." Maurice at 2.

4. Case reports

Petitioner submitted two case reports discussing patients who developed interstitial lung disease[7] following vaccination. In Watanabe et al., the authors discussed the case of a 75-year old female who was referred to the hospital with an eventual diagnosis of interstitial lung disease two weeks after a flu vaccine. *See* Ex. 14, Watanabe et al., *Influenza vaccine-induced interstitial lung disease*, 41 EUR. RESPIRATORY J. 2, 474-76 (2012) (filed as Ex. 14) (hereinafter "Watanabe"). There were no findings of infection, granuloma, or malignancy. *Id.* at 1. The authors stated that "based on the clinical course, a possible cause was influenza vaccination. The temporal relationship between influenza vaccination and clinical symptoms argued strongly for a causative role of this agent." *Id.* It was also noted that the ILD could not be explained by other causes, such as infection or vascular disease. *Id.*

In reviewing the literature, the authors noted five other possible cases of vaccine-induced ILD. Watanabe at 2. The average onset of disease was one to two days after vaccination in four

[7] Interstitial Lung Disease is "a heterogeneous group of noninfectious, nonmalignant disorders of the lower respiratory tract, affecting primarily the alveolar wall structures but also often involving the small airways and blood vessels of the lung parenchyma; slowly progressive loss of alveolar-capillary units may lead to respiratory insufficiency and death." *Interstitial Lung Disease*, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=70466&searchterm=interstitial+lung+disease (last accessed March 18, 2022).

patients, and six to ten days in the other three. *Id.* at 2. Of these patients, four had pre-existing lung conditions. *Id.*

Noting that the mechanism of drug-induced ILD is not well understood, the authors stated that in their patient, "immune-mediated reaction of the lung to the vaccine was suspected…" and that "[a]lthough data as to the sensitivity and specificity of the DLST [drug lymphocyte stimulation test] is lacking and it is not always helpful for the diagnosis of drug hypersensitivity, in this case there was immune-mediated reaction of T-cells to the vaccine." *Id.*

In a second case report by Biru et al, the authors discussed the case of a 37-year old male who was suspected to develop ILD following receipt of the Tdap vaccine. Biru et al., *Rare Case of Rapidly Progressive Interstitial Lung Disease Following Adult Tetanus, Diphtheria, and Pertussis (TDAP) Vaccination*, 197 AM. J. RESPIRATORY CRITICAL CARE MED. A6582 (2018) (filed as Ex. 60) (hereinafter "Biru"). Biru reported on a patient who presented with "dyspnea on exertion and worsening hypoxia for 1 month." Biru at 1. The patient received the Tdap vaccine and within a "few days he developed myalgias, anorexia, fatigue and rash." *Id.* One week later, he presented to the emergency department with "possible Type 3 hypersensitivity to vaccine." *Id.* In discussing the potential cause of the patient's ILD, the authors stated that "there are a few reported cases of HPV vaccine-related pneumonitis [but]…this may represent the first reported cause of Tdap vaccine related acute pneumonitis." *Id.* The authors noted further that the "temporal relationship between vaccination and the onset of pneumonitis and respiratory failure in this case cannot be ignored…. The patient may have had an underlying connective tissue disease associated ILD that exacerbated in the setting of up-regulation of his immune system following vaccine exposure." *Id.*

While case reports are not robust evidence, they do constitute some evidence with which a petitioner can meet her burden in the Vaccine Program. *See Contreras v. Sec'y of Health & Hum. Servs.*, 107 Fed. C. 280 (Fed. Cl. 2012); *see also Capizzano* 440 F.3d at 1325-26. This is especially true given that bronchiolitis obliterans is an "exceedingly rare" condition. It is difficult to imagine how a study could be sufficiently powered to detect instances of bronchiolitis obliterans arising as a result of flu vaccination administered when a patient was suffering a sub-clinical respiratory tract infection. As a result, case reports of this rare condition following vaccination "carry more significance than I might otherwise accord them." *See Raymo v. Sec'y of Health & Human Servs.*, No. 11-0654V, 2014 WL 1092274, at *21 (Fed. Cl. Feb. 24, 2014) (finding that case reports were more persuasive when the complained of disease was rare).

5. Respondent's Contentions

Respondent made several additional points in opposition to Petitioner's causation theory. Dr. Byers testified at hearing that he recommends all his patients with constrictive bronchiolitis receive the flu vaccine. Tr. at 123. While this point does suggest that patients with bronchiolitis obliterans do not see any worsening in their condition after vaccination (once they have already developed this disease), it does not address Petitioner's theory of causation in this case – that a sub-clinical viral infection plus vaccination caused Petitioner's disease process to begin.

In advancing her theory that the flu vaccine worked in concert with the URI to cause the development of bronchiolitis obliterans, Petitioner noted that her doctors likely would not have administered the flu vaccine had they known she was sick. Dr. Gershwin testified as to why it is ill-conceived to vaccinate a patient under these circumstances. "I wouldn't want to exacerbate activated immune cells. I want the immune cells to do only what they are supposed to do. I don't want them to become uncontrolled. I don't want to imbalance homeostasis." Tr. at 101. Dr. Gershwin opined that in Ms. Antalosky's case, adding the additional immune stimulation of the vaccine on top of her viral infection resulted in a shift from protection into damage. *Id.* Dr. Byers generally agreed that vaccination is not recommended if a patient is sick. He testified as follows:

> if someone has an active process going on … we would not give a vaccination at that time because you sort of want to let the body take care of what's going on first before giving the vaccination. So you want to make sure that they are otherwise in a homeostatic condition, if you will, sort of at baseline. So it's not our practice to vaccinate people if they are acutely ill.

Tr. at 160. The fact that both experts agreed that it is not advisable to vaccinate someone who is sick (or acutely ill) provides additional support for Petitioner's theory in this case.

The Fujinami article also provides support for this theory. Fujinami stated that "any given individual may be repeatedly exposed to a potential immunogen without any untoward consequences; but that under some circumstances, for example, if the person had a viral infection at the time of exposure, infection would alter the immunological environment in which the antigen was encountered, leading to a profound immune response." Fujinami at 83.

Respondent's position at hearing was that Petitioner's viral illness alone caused her to develop bronchiolitis obliterans. In fact, both experts agreed that bronchiolitis obliterans can develop as a result of respiratory viral infections. First Byers Rep. at 3; Tr at 51 (Dr. Gershwin testifying that viral infections can produce bronchiolitis obliterans); *see also* Li et al., *Post-infectious bronchiolitis obliterans in children: a review of 42 cases*, 14 BMC PEDIATRICS 238, 1-6 (2014) (filed as Ex. C5) (hereinafter "Li"). While it is understood that bronchiolitis obliterans develops after respiratory viral infection, experts in the field do not understand why or how this occurs. *See, e.g.*, Li et al., (noting that "the pathogenesis of [post-infectious bronchiolitis obliterans] is still not completely understood."); *see also* Tr. at 126 (Dr. Byers stating that "I don't know why the virus infection that she had, whatever virus that was, would lead to constrictive bronchiolitis."). Although Dr. Byers opined that Petitioner's flu vaccine "was irrelevant in the development of her lung disease" (Tr. at 125) he also testified that "It's very difficult to understand the mechanistic basis for diseases that are exceedingly rare." Tr. at 115. Ultimately, Dr. Byers concluded as follows: "Hypothetically, if she didn't have a respiratory virus infection, if she had the flu vaccination and then developed this lung disease without any other sort of inflammatory stimulus going on in her airways, I think it would be a different discussion." Tr. at 171.

It is settled that "close calls" as to the causal link between a vaccine and the injury asserted by a Petitioner should be resolved in favor of the petitioner. *Knudsen by Knudsen*, 35 F.3d at 549. I find this case presents a close call with respect to the first *Althen* prong. I conclude that the medical literature and case reports filed in this case, along with the opinion of Dr. Gershwin

provide preponderant evidence with respect to the first *Althen* prong.

C. *Althen* Prong Two

Under *Althen's* second prong, a petitioner must "prove a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." *Id.* A petitioner is not required to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." *Id.* (omitting internal citations). *Capizzano*, 440 F.3d at 1325. Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second *Althen* prong.

1. Petitioner Had a Sub-Clinical Viral Infection at the Time of Vaccination

The first step of Petitioner's causation theory requires the existence of an active, but sub-clinical viral infection in Petitioner's lungs at the time of vaccination. During the hearing, Dr. Gershwin stated that Petitioner's wheezing the day after her flu vaccination represented a sign of the lung infection. Tr. at 44. Dr. Gershwin further testified that the nasal symptoms she experienced following the wheezing were also suggestive of some sort of viral infection. *Id.* He also noted that prior to Petitioner showing signs and symptoms of illness, her body would have already been fighting the viral infection, during a time period he called the "incubation period" – the time between when the virus first enters the host and when the signs and symptoms begin. *Id.* at 53. It would be during this time period that Petitioner was suffering from a sub-clinical infection.

In her affidavit, Petitioner averred that she was in good health prior to her vaccination in October of 2014. Ex. 11 at 1. The day after vaccination, she "started to notice a slight wheeze that [she] never had before." *Id.* About four days later, she "started to have a dry cough and [she] noticed [she] was getting out of breath when [she] was doing normal activities like having a conversation or walking around [her] house. *Id.*

Petitioner also testified at the hearing that the day after she received the vaccine, she started wheezing. Tr. at 15. She stated that she specifically remembered that it was the day after her vaccination. *Id.* She testified that when she started wheezing, she said to herself, "What's going on here? I thought to myself, okay, maybe I'm getting a head cold or something. And then I thought to myself, wouldn't that be funny; I just got the flu shot yesterday; everybody says they end up getting the flu from the flu shot." *Id.* She estimated that "maybe two weeks later" she experienced nasal symptoms which lasted between one and two weeks, then disappeared, leaving her with wheezing, coughing, and shortness of breath. *Id.*

In his second expert report, Dr. Byers also acknowledged that Petitioner may have acquired a respiratory infection sometime around September-October 2014. Second Byers Rep. at 3. ("It is much more likely that a respiratory virus infection that she acquired in September-October 2014…."). At the hearing, Dr. Byers further stated that he believed that Petitioner suffered from a

viral infection around the time of her vaccination.[8] *See generally* Tr. at 130-31, 157-58. In particular, Dr. Byers noted that "the sinus congestion, draining and cough would be certainly a viral syndrome of upper respiratory tract at least. With the presence of shortness of breath, I would call that a lower respiratory tract infection as well." Tr. at 131.

Petitioner's medical records show that her treaters noted her as an "appropriate historian" of her own medical history. Ex. 1 at 1. Several of the medical records support Petitioner's testimony that she began wheezing the day after vaccination.

On November 29, 2014, Petitioner presented to Jill E. Nye, D.O., with complaints of coughing and shortness of breath. Ex. 49 at 1. Dr. Nye stated that Petitioner "started with a normal head and chest cold about 6 weeks ago." *Id.* Dr. Nye noted that "most of that dissipated within a few weeks but she has been left with this cough. …she has been feeling extremely short of breath." *Id.* Dr. Nye also noted that she was "quite surprised by the amount of lung tightness and wheezing in this non-asthmatic patient. More than likely a viral infection has set off [reactive airway disease]. *Id.* at 2. This record places onset of Petitioner's viral infection sometime in mid-October.

On December 17, 2014, Petitioner visited Dr. Paul F. Simonelli, who noted that Petitioner "developed worsening wheezing, chest tightness and dyspnea following a flu vaccination…." Ex. 4 at 5.

On December 18, 2014, Petitioner presented to Dr. Thomas Hood in the pulmonary outpatient clinic for an evaluation of shortness of breath. Ex. 4 at 1. In the medical history, Dr. Hood noted that Petitioner had "been having shortness of breath for the last several weeks. She received a flu vaccine in [on October 15, 2014] and noticed a slight wheeze since getting the injection." *Id.* Dr. Hood noted that Petitioner had "head cold symptoms" approximately "1-2 weeks prior to Thanksgiving."[9] He also noted that the shortness of breath "started and persisted since the end of November." *Id.* This record appears to place onset of wheezing the day of or the day after vaccination, and her nasal congestion anywhere from November 13, 2014 - November 20, 2014. This tracks closely with Petitioner's affidavit and testimony, where she stated that she began wheezing the day after vaccination and began having nasal symptoms "maybe two weeks later."

In addition to these records which clearly show Petitioner's wheezing beginning within a day of her vaccination, several of Petitioner's medical records are vague as to the onset of her symptoms and provide some support for onset of her viral infection prior to her vaccination.

On December 1, 2014, Petitioner visited Dr. Kristy Holecko. Ex. 8 at 2. Petitioner presented for an evaluation of shortness of breath. *Id.* Dr. Holecko noted that "she had a URI that started several weeks ago and has developed cough and shortness of breath subsequent to that." *Id.* While this record is unclear as to the onset of Petitioner's symptoms, I note that this record

[8] Dr. Byers further stated that he had no reason to doubt Petitioner's testimony that her wheezing started the day after her vaccination.

[9] Thanksgiving 2014 was on November 27, 2014.

specifically refers to the cause of Petitioner's respiratory symptoms as an upper respiratory infection.

On the same date, Petitioner was seen at the Gsach-Geisinger Shamokin Area Community Hospital emergency department. Ex. 8 at 6. Petitioner presented with "c/o persistent cough, shortness of breath, and wheezing since last 3-4 weeks." *Id.* Dr. Gunjan Munjal noted that Petitioner stated that her symptoms "started few weeks back and [became] progressively worse with cough and shortness of breath…." *Id.* He also noted that Petitioner had suffered from a "runny congested nose with sore throat and dry cough." *Id.* This record does not provide a timeline for her nasal symptoms. I also note that the record leaves unclear when Petitioner's symptoms started, as directly after saying Petitioner presented with cough, shortness of breath, and wheezing "since 3-4 weeks", the provider notes also indicate that Petitioner's symptoms "started [a] few weeks back." I therefore give this record less weight than other clearer records when considering the onset of Petitioner's viral symptoms.

Labs conducted following Petitioner's admission to the emergency department were "negative for all analytes tested…[including] for influenza A virus (H1, H3, 2009 H1 and non-subtypeable), influenza B virus, Respiratory Syncytial virus, Parainfluenza virus types 1, 2, 3, and 4, Human Metapneumovirus, Rhinovirus, Adenovirus, Coronaviruses: HKU1, NL63, 229E, and OC43, Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae." Ex. 8 at 13.

Both Petitioner's and Respondent's experts stated during the hearing that the usefulness of this lab test was limited. In particular, Dr. Byers stated he would not have expected to see a positive result from Petitioner's tests because "she didn't have [sinus congestion, nasal drainage, rhinitis] when she was in the hospital." Tr. at 130. Dr. Byers continued on to say that "the fact that [viruses] weren't present when [Petitioner was] tested doesn't mean she did not have a virus." *Id.*

On March 26, 2015, Petitioner visited Nurse Practitioner James Mendez. *Id.* In a patient-given medical history, Mr. Mendez wrote that "Lisa describes that she was in her [usual state of health] until October [15,] 2014 when she received her flu shot. A few days later, she developed cough and worsening dyspnea with wheezing." *Id.* A medical history taken by Dr. Vivek Ahya on the same date stated that "Lisa reports that she was in her usual state of health until October 2014. At that time, she developed respiratory viral infection symptoms – cough, wheezing, and dyspnea." *Id.* at 11. These records appear to place onset of Petitioner's symptoms anywhere from the day after the flu shot to a few days after her shot.

Petitioner's medical records largely follow the same pattern – wheezing, then nasal symptoms, and finally shortness of breath, within a three-week period. Several records place onset of Petitioner's symptoms almost exactly in the middle of October – when she received her vaccination. In addition, Dr. Byers acknowledged that Petitioner's nasal symptoms were likely evidence of an upper respiratory infection and that she clearly suffered from a viral infection between vaccination and her hospital visit on December 1, 2014. Petitioner's affidavit and testimony are also consistent with her medical history of wheezing shortly after the vaccination. Although not every medical record is clear on the onset of Petitioner's symptoms, the most contemporaneous record, from November 29, 2014, indicates that Petitioner's symptoms began in

mid-October. I therefore find that, under a preponderance of the evidence standard, Petitioner was suffering from a viral infection at the time of her vaccination. This active but sub-clinical respiratory infection is an essential element of Petitioner's theory of causation.

2. Proof of Specific Biological Mechanisms is not Required

Respondent contends that Petitioner is unable to support her bystander activation theory with evidence from her medical records. *See* Resp't's Post-Hearing Brief at 10. In addressing this issue at hearing, Dr. Gershwin explained that:

> [P]eople are unable in a clinical setting to do the type of immune analyses that I have shown existed in the literature. Meaning, there is no one in that pathology department that did anything more than look at it under a microscope. They didn't do any cytokine analysis because they can't. … They didn't do any study of the trapping of lymphocytes because that would be unethical.

Tr. at 87. He summarized by opining that, "It's all based on molecular and cellular definitions of what's happening at the level of the immune system individual cells." *Id.* Respondent rightly points out that there is no evidence from Petitioner's medical records showing that Dr. Gershwin's causation theory occurred in this case in the manner in which he described it. However, Petitioner is not required to make such a showing. *See Knudsen*, 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

3. Petitioner's Treating Physicians

In weighing evidence, special masters are expected to consider the views of treating doctors. *Capizzano*, 440 F.3d at 1326. The views of treating doctors about the appropriate diagnosis are often persuasive because the doctors have direct experience with the patient whom they are diagnosing. *See McCulloch v. Sec'y of Health & Hum. Servs.*, No. 09-293V, 2015 WL 3640610, at *20 (Fed. Cl. Spec. Mstr. May 22, 2015).

I note that several of Petitioner's medical records document a sensitivity or allergy to the flu vaccine. *See* Ex. 16 at 344-45 (noting "Reason Not to Give Vaccine Allergy/sensitivity to influenza vaccine"); Ex. 44 at 69; Ex. 46 at 142; Ex. 47 at 22; Ex. 48 at 161; Ex. 45 at 4; Ex. 48 at 270 (listing influenza vaccines as an allergy that cause lung damage); Ex. 44 at 76; Ex. 46 at 62; Ex. 46 at 94; Ex. 46 at 137; Ex. 46 at 156; Ex. 47 at 1; Ex. 48 at 88; Ex. 48 at 130; Ex. 48 at 137 (noting influenza vaccines as an allergy).

Petitioner visited Dr. Simonelli, a pulmonologist on February 18, 2015. Ex. 5 at 100. In discussing her constrictive bronchiolitis diagnosis, Dr. Simonelli noted that "the cause of her bronchiolitis is not known, though the temporal relationship to her receiving a flu vaccine is provocative." Ex. 6 at 2. Although this comment does not constitute an affirmative link between vaccination and Petitioner's bronchiolitis obliterans, it does support Petitioner's assertion in her affidavit that Dr. Simonelli told her he believed the flu vaccine caused her condition. She averred,

"Dr. Simonelli told me that the most likely cause for my lung disease was a reaction to the flu shot I received in October." Ex. 11 at 2.

Petitioner was admitted to the University of Pennsylvania Hospital on May 19, 2015, due to increased need for oxygen and increased dyspnea. Ex. 6 at 23. After undergoing several tests and procedures, she was discharged on May 27, 2015. *Id*. at 24. Petitioner's discharge summary indicated that Petitioner had biopsy proven bronchiolitis obliterans that was "suspected to have an underlying autoimmune etiology (response to flu immunization, +ANA)." *Id.* This notation in the medical records indicates that Petitioner's treating doctors at Penn believed that her flu vaccine caused her condition.

While this evidence does not involve a treating physician articulating a theory of causation regarding how the flu vaccine caused Petitioner's bronchiolitis obliterans, it still demonstrates that her treating physicians at the University of Pennsylvania, a prestigious and nationally recognized hospital, believed the flu vaccine caused Petitioner's illness. There is also evidence that Dr. Simonelli considered a link between Petitioner's flu vaccine and her condition. Additionally, Petitioner's treating doctors listed the flu vaccine as an allergy in her medical records. I find that the opinion of Petitioner's treating doctors is persuasive evidence with respect to whether Petitioner's flu vaccine did in fact cause her injury. Accordingly, I find that Petitioner has presented preponderant evidence in support of the second *Althen* prong.

D. *Althen* Prong Three

The timing prong contains two parts. First, a petitioner must establish the "timeframe for which it is medically acceptable to infer causation" and second, she must demonstrate that the onset of the disease occurred in this period. *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013).

1. Bronchiolitis Obliterans Develops Within Weeks of a Triggering Event

During the hearing, Dr. Byers stated that bronchiolitis is a "rapidly progressive" disease, and the onset of bronchiolitis can develop "weeks to months" after a respiratory infection. Tr. at 100, 117. He further stated that a respiratory infection suffered in October/November by Petitioner would appropriately fit the timeline for "bronchiolitis on pathology that became symptomatic by the end of December." *Id.* at 131. Dr. Byers also stated that "wheezing and shortness of breath and chest tightness, all of those manifestations she had in the end of November and early December are symptoms of constrictive bronchiolitis." Tr. at 140.

Based on this testimony, therefore, I find that it is medically acceptable for bronchiolitis obliterans to develop "within weeks to months" of a triggering event.

2. Petitioner's Theory of Causation Places Activation of Cytokines/Bystander Activation "within days" of Vaccination

During his testimony, Dr. Gershwin stated that cytokine production begins "early" in the lung during a viral infection. Tr. at 55; *see also* Laura Denney & Ling-Pei Ho, *The Role of Respiratory Epithelium in Host Defence Against Influenza Virus Infection*, 41 BIOMEDICAL J. 218-33 (2018) (filed as Ex. 65) (discussing how cytokine production is one of the first steps taken by the immune system during infection). Similarly, following influenza vaccination, Dr. Gershwin stated that cytokine production is one of the first processes the body undergoes. Tr. at 57.

Regarding bystander activation, Dr. Gershwin stated that "it would start within days." Tr. at 100. Dr. Gershwin's theory of the timing of bystander activation is supported by the medical literature. In Suwannasaen et al., the authors compared the kinetics of IFN-y production of bystander T cells with innate NK cells and activated specific T cells. *See* Suwannasaen, et al., *Bystander T Cells in Human Immune Responses to Dengue Antigens*, 11 BMC IMMUNOLOGY 47 (2010) (filed as Ex. 56). The authors noted that IFN-y cells "could be detected as early as 12 [hours]" after stimulation of bystander cells. *Id.* at 3. Furthermore, the "proportion of bystander and specific T cells from 18 samples was equal after 24 h[ours]." *Id*; *see also* Maurice at 4 (noting that bystander activation was detected within 24 hours of immunization).

Dr. Gershwin also stated that following the initial bystander activation, the reaction would "continue to become exacerbated… [and eventually] uncontrolled." Tr. at 55. In the Maurice article, the authors noted that "at least some bystander-activated T cells remain located at…immune activation sites for days and temporally and spatially overlap with incoming Ag-specific T cells." Maurice at 2. These articles coupled with Dr. Gershwin's testimony support the initiation of bystander activation within days of vaccination.

3. Petitioner Developed Bronchiolitis Obliterans Within a Medically Appropriate Time Frame

Petitioner's disease course fits the timeline discussed by both Dr. Gershwin and Dr. Byers. On October 15, 2014, Petitioner received her flu vaccination while suffering from a subclinical respiratory viral infection. The next day, she experienced wheezing, a symptom of the respiratory infection. Approximately two days later, Petitioner had a hard time catching her breath after climbing stairs and began coughing. Tr. at 16., *see also* Ex. 49 at 1. Two weeks later, at the beginning of November, Petitioner had nasal symptoms which resolved by the end of the month. *Id.* By the end of November/beginning of December, Petitioner was left with coughing, wheezing, and shortness of breath. These symptoms were the manifestations of bronchiolitis as described by Dr. Byers in his testimony. It is therefore reasonable to believe that during that time period, Petitioner's immune cells were activated via bystander activation, which eventually led to an uncontrolled reaction causing bronchiolitis obliterans.

Based on the testimony from Dr. Byers outlining the typical onset of bronchiolitis obliterans, and the fact that Petitioner's disease progression fits within this timeline, I find that Petitioner's bronchiolitis obliterans began within a medically appropriate timeframe relative to her vaccination.

VII. CONCLUSION

Based on the foregoing, I conclude that Petitioner has met her burden of proof under *Althen*. Accordingly, Petitioner is entitled to compensation. An order regarding damages will issue shortly.

IT IS SO ORDERED.

s/ Katherine E. Oler
Katherine E. Oler
Special Master